GRIGORE T. POPA UNIVERSITY OF MEDICINE AND PHARMACY IASI

Habilitation Thesis

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The inner ear's story: from deafness to hearing, from dizziness to balance - an integrative approach

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ABSTRACT

The habilitation thesis entitled ”The inner ear’s story: from deafness to hearing, from dizziness to balance - an integrative approach” reflects study and research activities from a period of over 20 years of my career and represents the synthesis of one of my directions of postdoctoral scientific research, oriented to the functional and pathological aspects of the inner ear, as well as to the modern methodology of rehabilitation of its functions. Hearing and balance, essential functions that condition language learning, school and social inclusion, cognitive and locomotion development, have sensorial segments in the inner ear. The importance of these functions justifies an increased interest in research on their physiology, the diagnosis of specific diseases and especially for the therapeutic possibilities of rehabilitation.

According to the recommendations of the National Council for the Attestation of University Degrees, Diplomas and Certificates (CNATDCU), I structured the habilitation thesis in the sections presented below.

Section I, after exposing of a selection of my achievements in the medical professional activity, in the academic one and in the scientific research, presents the main study directions to which I contributed and the synthesis of the most important 47 articles published in journals indexed in both Thomson ISI Web of Science Core Collection (14), as well as in international databases (33). The personal scientific contributions followed an integrative approach to the inner ear’s topic, referring to both cochlear and vestibular function and their interferences.

Chapter I.1 presents the results of studies on the impact of congenital hearing loss and the methodology for diagnosing deafness. The publications of our team in the field of early detection and diagnosis of deafness, along with involvement in specific organizational activities, contributed to the creation of the National Screening Program for Newborn Deafness in Romania (2019). The results of our studies and their practical applications in the field of cochlear implants have favored us in the development of a cochlear implant center, which has become a leader in Romania. The research of the diagnostic evaluation of speech disorders related to hearing loss, contributed to the realization of the first and only set of standardized and clinically validated Romanian audiometry vocal tests (RoVoIs), currently being approved by OSIM. The results of studies on the genetic diagnosis of deafness allowed the publication of the first data on the genetic profile of the deafness in northeastern Romania. As part of a grant I won through a competition, I also addressed diseases in the spectrum of auditory neuropathies, a very current research direction worldwide. This chapter brings together the results of 3 ISI indexed articles, 1 ISI proceedings article and 10 indexed articles in international databases.

Chapter I.2 includes the results of the most important research related to the treatment of deafness with implantable hearing aids, synthesizing 5 ISI indexed articles, 1 ISI proceedings article and 15 indexed articles in international databases. The publications refer to the electro-neural hearing loop created between the cochlear implant and the human auditory neural system, to the phenomenon of maturation of the auditory nerve under electrical stimulation (a global reference study) and to the efficiency of deafness treatment by cochlear implant and bone anchoring hearing aids. The research I participated included also the study of the results of cochlear implant treatment in rare cases - inner ear tumors and cochlear malformations, as well as the evaluation of the reliability of cochlear implants in international and national multicenter research. One of the most important articles included in this chapter presents the conclusions of a unique international research concluded with the publication of a global consensus on the methodology of cochlear implant programming in all manufacturing industries.

Chapter I.3 brings together research on the vestibular compartment of the inner ear. This direction of study includes the diagnosis of vestibular pathology, from the anamnestic algorithm

to the objective methodology of vestibular evaluation: evoked myogenic vestibular potentials and computerized dynamic posturography. The experience gained in the direction of studies on salivary stress markers, combined with that of vestibular diagnosis by caloric tests allowed me to initiate a study on the interactions between the vestibular system and the neuro-vegetative system, the effects of vestibular stress on cardiovascular reactivity being published in an ISI article. Also, there are presented the results of research on betahistine treatment strategies in vestibular vertigo in an international muticentric study and the results of betahistine treatment combined with transtimpanically administered dexamethasone in Meniere's disease. This chapter presents the synthesis of 2 ISI indexed articles and 5 indexed articles in international databases.

Chapter I.4 reflects a very special concern in my work, referring to the interferences between the functions of the inner ear: auditory and vestibular. The research we initiated and carried out in the cochlear implant center started from the need to know the status of the vestibular function of the young children who were to be cochlear implanted. Implantation at the age of less than 1 year old can compromise gait development if it results in vestibular bilateral damages. The results of the research of these interactions between the cochlear and vestibular segment in the case study of deaf patients after cochlear implantation intervention were published in the form of 2 ISI indexed articles and 3 indexed articles in international databases, our studies are among the very few published so far on this topical issue, especially in children. The purpose of this knowledge is to optimize the treatment by cochlear implant with minimal vestibular damage.

Section II. In terms of medical activity, I propose to expand the audiology service I lead and increase patients' access to new means of diagnosis and treatment of ear pathology, with emphasis on outpatient therapies and care for patients with cochlear implants and bone anchored hearing aids. Academically, in addition to completing the teaching activity and textbook projects for students and residents, I propose the continuous organization of training courses in the field of audiology and vestibulogy, in conjunction with the development of the Romanian Society of Audiology and Communication Pathology whose founder member I have been since 2014. Also, a very important project for my career is the relaunch of the Bachelor of Audiology and Hearing Aids studies within the “Grigore T Popa” University of Medicine and Pharmacy in Iași. In the scientific research I have in mind the co-optation of doctoral students interested in the study of the inner ear, presented in this habilitation thesis, but also in other research directions I have worked on. I intend to continue research on the pathology, diagnosis and rehabilitation of internal ear functions, mainly through the technology of cochlear implantation and the future vestibular implant.

Section III includes the list of bibliographic references consulted for the elaboration of the thesis and the articles included in this synthesis.

REZUMAT

Teza de abilitare intitulată „Povestea urechii interne: de la surditate la auz, de la amețeli la echilibru - o abordare integrativă” reflectă activități de studiu și cercetare dintr-o perioadă de peste 20 de ani din cariera mea și reprezintă sinteza uneia dintre direcțiile mele de cercetare științifică postdoctorală, orientată către aspectele funcționale și patologice ale urechii interne, precum și către metodologia modernă de reabilitare a funcțiilor sale. Auzul și echilibrul, funcții esențiale care condiționează învățarea limbajului, incluziunea școlară și socială, dezvoltarea cognitivă și locomoția, au segmentele senzoriale în urechea internă. Importanța acestor funcții justifică un interes crescut pentru cercetările privind fiziologia lor, diagnosticul afecțiunilor specifice și mai ales pentru posibilitățile terapeutice de reabilitare.

Conform recomandărilor Consiliului Național pentru Atestarea Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU), am structurat teza de abilitare în secțiunile prezentate mai jos.

Secțiunea I, după expunerea unei selecții a realizărilor mele în activitatea profesională medicală, în cea academică și în cercetarea științifică, prezintă principalele direcții de studiu la care am contribuit și sinteza celor mai importante 47 de articole publicate în jurnale de specialitate indexate atât în Thomson ISI Web of Science Core Collection (14), cât și în baze de date internaționale (33). Contribuțiile personale științifice au urmărit o abordare integrativă a problematicii urechii interne, referindu-se atât la funcția cohleară, cât și la cea vestibulară și interferențe ale acestora.

Capitolul I.1 prezintă rezultatele studiilor despre impactul hipoacuziei congenitale și metodologia de diagnostic a surdității. Publicațiile colectivului nostru din domeniul detecției și diagnosticului precoce a surdității, alături de implicarea în activități organizatorice specifice, au contribuit la crearea Programului Național de Screening a Surdității la Nou-născut în România (2019). Rezultatele studiilor noastre și aplicațiile lor practice în domeniul implantului cohlear ne-au favorizat în dezvoltarea în Spitalul Clinic de Recuperare Iași a unui centru de implant cohlear devenit lider România. Cercetarea evaluării diagnostice a tulburărilor de limbaj legate de hipoacuzie, a contribuit la realizarea primului și singurului set de teste de audiometrie vocală în limba română standardizat și validat clinic (RoVoIs), aflat în curs de omologare la OSIM. Rezultatele studiilor privind diagnosticul genetic al surdității au permis publicarea primelor date despre profilul genetic al hipoacuzicilor din nord-estul României. În cadrul unui grant pe care l-am câștigat prin concurs am abordat și bolile din spectrul neuropatiilor auditive, direcție de cercetare foarte actuală la nivel mondial. Capitolul reunește rezultatele a 3 articole indexate ISI, 1 articol ISI proceedings și 10 articole indexate în baze de date internaționale.

Capitolul I.2 include rezultatele celor mai importante cercetări legate de tratamentul surdității prin proteze auditive implantabile, sintetizând 5 articole indexate ISI, 1 articol ISI proceedings și 15 articole indexate în baze de date internaționale. Publicațiile se referă la bucla auditivă electro-neurală creată între implantul cohlear și sistemul neural auditiv uman, la fenomenele de maturare a nervului auditiv sub stimularea electrică (studiu de referință la nivel mondial) și la eficiența tratamentului surdității prin implant cohlear și proteze cu ancorare osoasă. Cercetările la care am participat au inclus și studiul rezultatelor tratamentului prin implant cohlear în cazuri rare – tumori ale urechii interne și malformații cohleare, precum și evaluarea fiabilității implantelor cohleare în cadrul unor cercetări multicentrice internaționale și nationale. Unul dintre cele mai importante articole incluse în acest capitol prezintă concluziile unei cercetări internaționale unice încheiată cu publicarea unui consensus global asupra metodologiei de programare a implantelor cohleare din toate industriile producătoare.

Capitolul I.3 reunește cercetările privind compartimentul vestibular al urechii interne. Această direcție de studiu cuprinde diagnosticul patologiei vestibulare, de la algoritmul anamnestic la metodologia obiectivă de evaluare vestibulară: potențialele evocate vestibulare miogenice și posturografia dinamică computerizată. Experiența acumulată pe direcția de studii privind markerii salivari de stress, combinată cu cea a diagnosticului vestibular prin probe calorice mi-a permis inițierea unui studiu privind interacțiunile sistemului vestibular cu cel neuro-vegetativ, efectele stresului vestibular asupra reactivității cardio-vasculare fiind publicate într-un articol ISI. De asemenea sunt prezentate rezultatele cercetărilor privind strategiile de tratament general cu betahistină în vertijul vestibular în cadrul unui studiu internațional muticentric și rezultatele tratamentului cu betahistină combinat cu dexametazonă administrată transtimpanic în boala Meniere. În acest capitol se prezintă sinteza a 2 articole indexate ISI și 5 articole indexate în baze de date internaționale.

Capitolul I.4 reflectă o preocupare foarte specială în activitatea mea, referindu-se la interferențele dintre funcțiile urechii interne: auditivă și vestibulară. Cercetările pe care le-am inițiat și pe care le-am desfășurat în centrul de implant cohlear au pornit de la nevoia de cunoaștere a statusului funcției vestibulare a copilului mic ce urma să fie implantat cohlear. Implantarea la vârsta de sub 1 an poate compromite dezvoltarea mersului dacă se soldează cu deteriorarea vestibulului bilateral. Rezultatele cercetării acestor interacțiuni dintre segmentul cohlear și cel vestibular în cazuistica pacientului surd după intervenția de implantare cohleară au fost publicate sub forma a 2 articole indexate ISI și 3 articole indexate în baze de date internaționale, studiile noastre sunt printre foarte puținele publicate până în prezent pe această temă de actualitate, mai ales la copil. Scopul acestei cunoașteri este optimizarea tratamentului prin implant cohlear cu minimum de deteriorare vestibulară.

Secțiunea II. În planul activității medicale îmi propun extinderea serviciului de audiologie pe care îl conduc și creșterea accesului pacienților la noile mijloace de diagnostic și tratament a patologiei urechii, cu accent pe terapiile de ambulator și asistența pacienților cu implant cohlear si proteze cu ancorare osoasă. În plan academic, pe lângă perfectarea activității de predare și proiectele de realizare de manuale pentru studenți și rezidenți, îmi propun organizarea continuă a cursurilor de perfecționare în domeniul audiologiei și vestibulogiei, în conjuncție cu dezvoltarea Societății Române de Audiologie și Patologie a Comunicării a cărui membru fondator sunt din anul 2014. De asemnea, un proiect deosebit de important pentru cariera mea este relansarea direcției de studii de licență de Audiologie și Protezare Auditivă în cadrul Universității de Medicină și Farmacie ”Grigore T Popa” din Iași. În cadrul cercetării științifice am în vedere cooptarea doctoranzilor interesați de studiul urechii interne, prezentat în această teză de abilitare, dar și pe alte direcții de cercetare pe care am lucrat. Îmi propun continuarea cercetărilor privind patologia, diagnosticul și reabilitarea funcțiilor urechii interne, în principal prin tehnologia implantării cohleare și a viitorului implant vestibular.

Secțiunea III include lista referințelor bibliografice consultate pentru elaborarea tezei și a articolelor incluse în această sinteză.

OVERVIEW OF PERSONAL PROFESSIONAL, ACADEMIC AND SCIENTIFIC CONTRIBUTIONS

The academic didactic career in the medical field is complementary in most fields and specialties with the medical professional activity and with the research activity. Managing this trio of excellence is a challenge for anyone who wants such a career. Being a very good doctor, a dedicated teacher and an ambitious researcher with recognized results requires learning, involvement, time, dedication, passion, effort, team spirit and excellence - all being mandatory ingredients for a successful professional, academic and scientific path.

Professional achievements

I graduated from the Faculty of Medicine, General Medicine specialty in 1996 at the "Grigore T. Popa" University of Medicine and Pharmacy in Iași (graduate diploma no. 334 / 24.02.1997) and in 1998 I began residency in ENT specialty at the Clinical Rehabilitation Hospital from Iași. During this period, I went through the internships specific to the specialty and I became an ENT specialist in 2002 (Minister of Health Order no. 1030 of 20/12/2002), and in 2008 I became senior specialist ENT doctor (Minister of Health Order no. 1971 of 03/12/2008).

In the ENT clinic where I trained and I started my didactic career in 1998, the special concerns of the medical team for otology and for the deafness rehabilitation by cochlear implant determined me, after obtaining the title of specialist doctor, to focus my training on audiology overspecialization.

Starting with the year 2000, I was member of Prof. Dr. Dan Mârțu team, who performed the first cochlear implant in Romania and I contributed to the creation and development of the necessary structures for the national cochlear implant program functioning in our country.

In 2002 I won a clinical internship scholarship offered by Hospices Civils de Lyon, France and I was accepted in the Audiology and ENT Functional Explorations Service at the Emergency Hospital "Edouard Herriot" in Lyon, under the guidance of Prof. Dr. Lionel Collet, a remarkable academic personality with an impressive research activity. During the internship I also attended the courses of the **Interuniversity Diploma in Communication Pathology and Audiophonology**, which I graduated in 2003 (Diploma series 0ETRY 20020800 from 24/06/2004) at the "Claude Bernard Lyon 1" University.

In 2008 I obtained doctoral degree in medicine, defending the thesis ***"Clinical-electrophysiological correlations in sensorineural hearing loss"***, in ENT field, "Grigore T. Popa" University of Medicine and Pharmacy in Iași, scientific coordinator Prof. Dr. Dan Mârțu, confirmed by Ministry of Education and Scientific Research Order no. 4887 from 25/07/2008, obtaining the grade "Very good" and the distinction "Magna cum laude". My doctoral research is also the foundation of this habilitation thesis.

After returning from France, I focused my clinical activity on the pathology served by audiology and vestibulogy overspecialties and I created and developed the Audiology Department of the Clinical Rehabilitation Hospital Iași, with an organized infrastructure according to the model of similar service in France, where I trained. This has increased the diagnostic capacity of auditory pathology, as well as participation in two national programs related to deafness: the newborns hearing loss screening program and deafness rehabilitation with implantable hearing aids program (cochlear implant and bone-anchored prostheses). It also constituted a new training base in Iași University Center for the ENT specialty residents for the audiology training. The service is still unique in Moldova region, and its medical team performance attracts patients from all over the country. Together with colleagues from the ENT

Clinic we are constantly working for the development of the cochlear implant center in the Clinical Rehabilitation Hospital, which is currently a national leader. The arguments are reflected in the fact that we specialized in working with all the main existing devices in the field of implantable hearing aids (MedEl, Cochlear, Oticon, Advanced Bionics); our patients are both adults and children, from all over the country and from the Republic of Moldova. Fellow residents who come from other university centers for the internship within the residency request the audiology department; we also have participants from all over the country in the postgraduate courses we organize.

In 2008, the Clinical Rehabilitation Hospital from Iași was included in the National Newborns Auditory Screening Program - the pilot program stage, which took place until 2018 in this form. I was appointed coordinator of this national program in 2008-2018 period and I worked on the development of a protocol adapted to our system specifics, based on other European screening programs (Regional Manager - Coordinator PN VI Women's and Children's Health. Prevention of hearing impairments through neonatal screening - Clinical Rehabilitation Hospital Iași). The excellent collaboration with neonatal colleagues from public and private hospitals, brought Iași to the attention of the central authorities as the only center where it was possible to organize and carry out the newborns auditory screening program in a universal way (for all newborns) with coverage over 98% over 10 years. The model created together with colleagues in ENT and Neonatology was an example and a motivation for a national screening scale. I participated directly in the development of protocols for this national program over three years, as a consultant to the Minister of Health on this issue and I was part of the Minister of Health commission for public acquisition of hearing screening equipment for all maternity hospitals in the country. The project was completed and the activity had started throughout the country in 2019.

We initiated and developed over 10 years a partnership between the Clinical Rehabilitation Hospital through the Audiology Department, ”Vasile Pavelcu” Special Technological High School from Iaşi and the County School Inspectorate of Iaşi, which developed teacher education programs for auditory-verbal inclusion of deaf children receiving cochlear implantation treatment. As a result, at the ”Vasile Pavelcu” Special Technological High School, it was possible to create an early intervention center for deaf children, the first of its kind in the country.

Since 2007, I worked in the audiology service watching mainly the following medical professional concerns: hearing loss diagnosis in adults and children, management of patients with conventional and implantable hearing aids (cochlear implant, BAHA, intraoperative tests, activation of hearing devices and periodic functional adaptations, rehabilitation performance testing), newborn auditory screening, vestibular pathology diagnosis, treatment and rehabilitation in balance disorders, training of residents in the audiology module.

I constantly updated my medical professional knowledge and acquired new skills by attending training courses in the country and abroad (over 40 courses), including the course for "Project Manager" - May-June 2014, Iași and ”Informatics systems in medicine and public health ”- March-May 2013, Iași.

I was the Regional Coordinator of the Newborns Hearing Screening Program from 2006 to 2019 - carried out through the Clinical Rehabilitation Hospital Iași.

I am currently the Coordinator of the Audiology and Vestibulogy Department Iași from Clinical Rehabilitation Hospital of (since 2007), a member of the Medical Council of the Clinical Rehabilitation Hospital Iași and an alternate member of the hospital's Board of Directors.

Academic activity

After university graduating, I became a teacher by competition at the ENT Discipline, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi and I started teaching with students in 1998, in the ENT Clinic, Clinical Rehabilitation Hospital Iaşi. The course of my career in university education so far included the following steps:

- 1998 - 2001: ENT University Preparator
- 2001 - 2009: ENT University Assistant
- 2009 – 2018: ENT University Lecturer
- 2018 – present time: ENT Associate Professor

Thus, since 1998 and until now I have carried out teaching activities (internships and courses) and guidance at:

- Faculty of Medicine – General Medicine specialty and General Medical Assistance, in Romanian, English and, in recent years, French courses taught; between 2007 and 2010 I taught courses and practical works to students of Audiology and Hearing Rehabilitation specialty;
- Faculty of Dental Medicine (Romanian and English); I introduced an optional ENT emergency course for students of the Romanian and English language series;
- Faculty of Medical Bioengineering - Balneo-physio-kinetotherapist Specialty and Rehabilitation Bioengineering master program.

Between 2002 and 2007 I substantially contributed to the efforts to create a new direction of studies within the "Grigore T. Popa" University of Medicine and Pharmacy Iași: Audiology and Hearing Rehabilitation specialization, undergraduate studies. I taught in this section for the first time specialized courses in the second and third years of study (Prosthetic audiology and methods of prosthesis adaptation; Objective audiometry; Prosthetic audiology; Pediatric audiometry).

I coordinated numerous bachelor's theses in Romanian and French at the Faculty of Medicine (General Medicine, General Medical Assistance and Audiology and Hearing Rehabilitation specializations), the Faculty of Dental Medicine and the Faculty of Medical Bioengineering.

I coordinated the guidance of the residents within the ENT residency - between 2003 and 2008 within the ENT Clinic, and since 2008 within the Audiology Department for the audiology module, but also of the residents from other specialties: Orthodontics, Occupational Medicine.

I participated at the university request as commission member of the various exams and competitions: member in the commissions for obtaining the title of specialist and primary ENT doctor; member of the commission for competitions for teaching positions; member of doctoral admission commissions or doctoral study guidance commissions. I have repeatedly participated in the organization of admission exams at the "Grigore T. Popa" University of Medicine and Pharmacy Iași and residency competitions.

Academic and professional functions:

- Member in ENT Specialty Commission of the Ministry of Health (MH Order no. 726/13/05/2019) – since January 2017 – present;
- Territorial ENT Specialty Commission President for referral to treatment abroad (MH Order no 1141/28.09.2017) - since January 2017 – present;
- Coordinator of the National Deafness Rehabilitation through Implantable Prostheses Program in Romania (CNAS Order no. 454 din 08/05/2019) - since 2019 – present;
- Elected member in Department of Surgery II Council - ”Grigore T Popa” UMF Iași since 2016 – present;
- Elected member in University Senate of ”Grigore T Popa” UMF Iași (Decission no. 4/28.01.2020).

I am a member of professional organizations, some of which are founding members and / or members of the board of directors:

- since 1998 – member of *Romanian Society of Otorhinolaryngology* - Head and Neck Surgery;
- since 1998 - member of The Society of Physicians and Naturalists of Iaşi;
- since 2005 - co-founding member of Otoneurology and Audiology Section in The Society of Physicians and Naturalists of Iaşi;
- since 2012 - member of International Society of Audiology;
- since 2013 – member in Board of Directors of the Romanian Society of Pediatric Otolaryngology;
- since 2014 – founding member of Romanian Society of Neuro-Otology;
- since 2014 - founding member and president of Romanian Society of Audiology and Communication Disorders;
- since 2015 - national representative in EFAS (European Federation of Audiology Societies);
- since 2017 – member of French Society of ENT;
- since 2018 – member of International Bureau for Audiophonology (Cochlear Implant Commission and Auditory Deafness Screening Commission) – In present member of BIAP Board (2020) and President of Auditory Screening Commission (2019-2020).

Academic activity also meant contributions to the elaboration of textbooks and books for the medical educational process; thus, in the postdoctoral period I contributed to the elaboration of a "Course of otorhinolaryngological pathology and cervico-facial surgery" and 4 chapters in specialized books. I contributed to the development of the latest ENT guidelines of the Ministry of Health (2019).

Organizational capacity within the medical business and graduate and postgraduate education

I actively participated in the creation of Audiology and hearing rehabilitation section within the Faculty of General Medicine of UMF Iași.

I organized and coordinated the National Newborns Hearing Screening Program in Iași, achieving the performance of making Iași the only city in the country where universal neonatal hearing screening carried out in all maternity hospitals.

I am part of the Cochlear Implant team from the Clinical Rehabilitation Hospital Iași, within the National Cochlear Implant Program.

Currently, as Coordinator of the Audiology and Vestibulogy Department of the Clinical Rehabilitation Hospital Iași, I coordinate the training activity for the Audiology module within the ENT residency program.

Member of the Organizing or Scientific Committee of national and international scientific events:

- The days of the Clinical Rehabilitation Hospital conferences, Iaşi – 2010-2020 editions, annually;
- National Otorhinolaryngology and cervical-facial congresses and conferences, between 2010-2020;

I would like to note the most significant of these contributions to my career:

- Secretary-General of National ENT Congress 2010, 22-26 September 2010, Iași;
- President of The 2nd National Congress of Romanian Society of Pediatric Otolaryngology – Iași 2016;
- Member of National Scientific Committee of "The 42th Conventus Societas ORL Latina" - Sinaia, 6-9 September 2017;

- Vice-President of The 6th Romanian Pediatric ENT conference with international participation – Sovata, 25-28 September 2018;
- I initiated and organized First National Congress of Romanian Society of Audiology and Communication Disorders with international participation – Iași, September 2019

Organizational and coordinating postgraduate courses activities

I participated as a team member or coordinator in the organization and conduct of numerous courses and symposia aimed primarily at ENT doctors, neurologists, family physicians, neonatologists and pediatricians, including:

- International Course of Temporal Bone Surgery, Iaşi – between 1998 and 2002 – member of organizational team;
- Symposium "Updates in deafness diagnosis, treatment and rehabilitation in children", 7 October 2004, Iaşi – coordinator;
- Symposium "Treatment of hearing loss by hearing aid and cochlear implant", Iaşi, 21-22 April 2005 – coordinator ;
- Course of actualities in subjective and objective audiometry, Iaşi, 2007, 2008, 2009 editions – coordinator ;
- Course of ”Auditory-verbal rehabilitation in children with cochlear implant” – Iași, 26-27 May 2011 – coordinator ;
- Course of Audiology, July 2011, Iași – coordinator;
- Coordinator of a series of postgraduate courses with international participation: Vestibular system - questions and answers: the interdisciplinary approach to balance pathology –2014, 2015, 2016, 2018 editions.

Over the last 20 years, I have had the honor of being invited as a lecturer to multiple national and international events (conferences, congresses, courses, workshops) especially in the field of audiology and vestibular pathology.

Scientific activity

Scientific research initiated since the first steps in university life and has continued unabated to this day. Over the years, I have contributed to the formation and cultivation of scientific and academic relationships with other university centers such as Lyon, where I initially trained in audiology, or Rome, a relationship facilitated by the Erasmus program. I also collaborated with colleagues from Paris (France), Freiburg, Munich, Halle-Salle (Germany), Antwerp (Belgium), Sienna (Italy), São Paulo (Brazil) in carrying out scientific projects. These relationships reflected in some common scientific publications.

Personal contributions to research and development of scientific publications are presented below.

Participation in research funded by won grants:

- Internal Grant Director of “Grigore T. Popa” University of Medicine and Pharmacy Iași – 2015 competition - Optimal therapy protocol for deaf newborns with auditory neuropathy studying electroneural and audiological dynamic progress during the stimulation by conventional hearing aid and cochlear implant – No. 31585 din 23/12/2015;
- Member of the management team in the project POSDRU 56815, "Knowledge-based society" - Research Adviser - 2010 – 2011;
- Optimization of cochlear implant treatment in children with nonsyndromic autosomal recessive sensorineural hearing loss with mutations in the GJB2 gene - 2016-2018. Member of the research team - bilateral cooperation grant - “Grigore T. Popa” University of Medicine and Pharmacy Iași;
- "Training of communication skills in children with cochlear implant" funded by the "World through color and sound" fund - Orange Foundation: Project initiator: Association of people with hearing impairment "Listen to life" - 2015 - 2016 - Regional Manager for

Moldova - partner Clinical Rehabilitation Hospital Iași - project through national competition;

- Short-term expert in the project POSDRU /91/2.2/S/60655, CESPeT - Special educational requirements for all - member - since January 2011;
- Scientific research contract with the topic "Evaluation of speech perception and production skills in children receiving a cochlear implant", from September 20, 2005, no. of protocol: 2005PMS011, sponsored by Med-El, Innsbruck, Austria - participant - 2006/2007;
- Validation study for normal hearing children in Romania of the questionnaire: LittlEARS auditory questionnaire - July 12, 2005, PN 2005PMS008, sponsored by MED-EL electromedizinische Gerate GmbH - participant - 2005 - 2006;
- OSVaLD – Three-month observational study in patients with recurrent peripheral vestibular vertigo to evaluate the effect of Betahistine 48 mg / day on quality of life and symptoms of dizziness - early 2004 - clinical investigator.

Among the results that should be noted, I would add the realization of the first set of audiological tests for speech comprehension, *RoVoIs*, the product of this extensive research that materializes in an instrument that is being approved by Romanian Trade Marks Office.

I am a member of the editorial staff of the specialty publication *ORL.ro*, indexed in international databases (Index Copernicus) and I had been invited to perform peer-review analyzes for the following publications:

- The Scientific Bulletin of Electrical Engineering Faculty – SBEEF - Manuscript number: SBEEF-08-2018;
- Archive of clinical cases – 2020.
- Experimental and therapeutic medicine - Manuscript ID: ETM-2020-067 – 2020.

The main publications I have contributed totals:

- Indexed publications – Thomson ISI: 38 articles (18 articles as lead author, 11 co-author; 5 ISI proceedings articles as lead author and 4 co-author);
- BDI publications: 35 articles (17 as lead author and 18 coauthor) and another 28 in BDI publications supplements (14 lead author and 14 coauthor);
- 1 book (coauthor); 4 chapters in specialized books;
- H-Index – 8 in ISI Web of Science, having 180 citations and h index Google Scholar 10, having 386 citations.

The scientific and research activity has recognized by obtaining awards for a series of articles in which I was the main author or co-author and by awarding distinctions:

- UEFISCDI Prize for the article: Multicenter evaluation of Neurelec Digisonic® SP cochlear implant reliability - December 2013 - position 1166, list 2.
- UEFISCDI Prize for the article: Religion and medicine or the spiritual dimension of healing - December 2013 - position 2186.
- UEFISCDI Prize for the article: Distinct activation of the sympathetic adreno-medullar system and hypothalamus pituitary adrenal axis following the caloric vestibular test in healthy subjects - December 2018 - position 28, list 8.
- UEFISCDI Prize for the article: "Message from a turtle": otitis with Salmonella arizonae in children. - December 2018 - position 18, list 6.
- UEFISCDI Prize for the article: Morphofunctional evaluation of buccopharyngeal space using three-dimensional cone-beam computed tomography (3D-CBCT). - December 2018 - position 141, list 12.
- Diploma of Excellence from the Star of Hope Romania Foundation for the partnership model regarding the social inclusion of children and young people with special needs - 2017.

SECTION I
Scientific achievements

I.1. RESEARCHES REGARDING THE HEARING FUNCTION OF THE INNER EAR AND THE DIAGNOSTIC OF THE HEARING LOSS

The inner ear plays an extremely important role in the child's development, both in terms of hearing allowing language learning, communication skills, schooling, interpersonal interaction based on information exchange and cognitive development, and in terms of balance function (vestibular), which allows the development of gait control and preventing fall strategies and also has a role in cognitive development.

Hearing loss represents a frequently met sensorial handicap, which has a major and complex impact not only on the hearing-impaired person, but also on his family and society. The large number of hard-of-hearing persons justifies the acknowledgement of hearing loss as a public health issue, which oblige to appropriate health politics, to offer each hearing-impaired person health services like those in Europe.

The normal hearing at birth is one of the prerequisite conditions for speech acquisition. In this context, the early identification and treatment of deafness (the most frequent pathology encountered at birth – 1-3‰), represents one of the most important preoccupations in the public health policy in the developed countries.

Progress in medical technology has created new opportunities in the treatment of deafness, following three main directions of intervention.

One is early identification of children with hearing loss using electrophysiological methods (otoacoustic emissions – OAE, brainstem evoked response audiometry – BERA, auditory steady state response – ASSR). Such methods lead to the diagnosis of congenital deafness from the first days after birth (Johnson et al., 2005). They are noninvasive, and relatively easy to perform, and are highly available for usage as screening tools for deafness in maternities (Norton et al., 2000).

The second direction takes into account the new possibilities of deafness treatment either with powerful conventional digital hearing aids or with implantable prosthesis for middle ear (like BAHA - bone anchored hearing aid), for internal ear (cochlear implant) or for the eighth nerve (brainstem implants) (Davis, 1997; Rădulescu & Mârțu, 2007).

I.1.1. The principle of early detection and early diagnostic of the hearing impairement in children – the key and the golden standard in hearing loss rehabilitation

Congenital hearing loss is the most common disease present at birth (1-3/1000 newborns), but this problem is not obvious at birth or in early childhood, being an invisible disability, therefore timely diagnosis can not be made than by actively detecting hearing impairment. Universal newborn hearing screening (UNHS) is the only method we can identify infants with possible hearing problems, and they should be sent to audiology centers for certainty diagnosis and quantification of hearing loss. Neonatal hearing screening is the cheapest of all possible screening tests at birth and is a simple, non-invasive, short duration procedure. It involves only the existence in the maternity ward of a test equipment and two or three trained persons (coordinating doctor responsible for the control and compliance with procedures and nurses performing the tests).

In Romania, the National Newborn Hearing Screening Program began as a pilot program in three maternity hospitals in the country and an audiological diagnostic center.

Currently, with the support of the authorities, the national coverage of this program is achieved, by allocating by the Ministry of Health the necessary funds for the endowment with screening equipment of all maternity hospitals in the country, intensive care units in pediatric hospitals, and of audiological diagnostic centers, in order to standardize the data and transmit them to the National Electronic Register of auditory screening, launched by GovIT Hub, (http://ithub.gov.ro/2016/12/06/rensa-registrul-electronic-national-de-screening-auditiv).

I.1.1.1. The impact of congenital hearing loss and comorbidities in children – the role in the delay of speech development

Background

Congenital hearing loss, along with other sensory disabilities, has a significant negative impact on the child's development. The severity of the hearing loss, especially if not rehabilitated by appropriate surgical or prosthetic methods, shapes a child's development from multiple points of view. From an auditory point of view, the hearing-impaired child can be anywhere between deafblindness and defective language, but to these impediments are added the difficulties of integration into school communities, limited academic progress and, last but not least, frustrations and lack of self-respect. Generally, about 10% of the country's population suffers from various degrees of hearing loss. Most forms of deafness are not medically or surgically treatable, but are almost all recoverable by conventional hearing aids or implantable hearing systems. Without having a real record of the number of hearing-impaired people in Romania, an estimate based on epidemiological data from the literature and research in the field (doctoral or bachelor's theses) reveals the following situation for Romania:

- over 400 hearing-impaired newborns annually (1-3 ‰ live newborns) have profound bilateral deafness, at which there is a risk of becoming double disabled (deafblind) in the absence of early detection and therapeutic intervention (cochlear implant);
- about 2 million people (10%) of the country's population have hearing loss.

This large number of people with hearing impairments justifies the appreciation of hearing loss as a public health problem, which imposes specific health policies to provide each hearing-impaired patient health services at European level.

Congenital, perinatal or perlingual hearing loss causes severe problems in the language learning process, difficulties that are overcome in a fairly long time compared to children with normal hearing. The condition for a satisfactory evolution is the rehabilitation of the hearing deficit by hearing aid or cochlear implant.

Worldwide statistical studies estimate that the prevalence of mental retardation in the general population is 1%. Mild mental retardation has a prevalence of 0.4-0.6% in the general population, and moderate, severe and profound mental retardation together have a prevalence of 0.4%. Other studies indicate a prevalence of about 3% of the population for people with mental retardation, estimated by the WHO for Europe and North America. Over 85% of all cases of mental retardation are mild forms. Children with mental retardation may associate many somatic and psychiatric disturbances and also hearing impairment in 10% of cases. However, for children with mental retardation, a delay in speech will be noted. Many children have dyslalic speech and a reduced vocabulary. They understand basic speech, but they are not always accessible to more complex verbal expressions. Comorbidity with hearing loss will result in a more difficult language development in these children, requiring a collaborative team with psychiatrist, ENT specialist, psychologist, speech therapeut, with the earliest detection of sensory impairment and, as much as possible, adjusting it to allow the development to the maximum capacity of these children.

Genetic discoveries, etiopathogenic research and the general development of medical sciences bring a new perspective to understand the etiology and issues of this pathology and

open the perspective of integration and social acceptance of these individuals (Ghiorghe et al., 2009).

Main articles published in this field:

- Mădălina Georgescu, Violeta Necula, **Sebastian Cozma**. Impactul hipoacuziei. (The impact of hearing loss). *ORL.ro.* 2016; 33(4): 64-65. ISSN 2067-6530
- Andreea Silvana Szalontay, Alexandra Boloş, **Sebastian Cozma**. Comorbiditatea: întârziere mintală, hipoacuzie, tulburări de limbaj. (Comorbidity: mental retardation, hearing loss, speech disorders). *ORL.ro.* 2016; 33(4): 44-48. ISSN 2067-6530

Scientific contributions /Clinical implications:

- The interdisciplinary research together with fellow psychiatrists allowed the first topical study in Romania on language development delays in children with the association of hearing loss with neuro-psychiatric pathology, especially with autism and mental retardation.

Inroduction

According to the "Diagnostic and Statistical Manual of Mental Disorders", the essential element of the delay in mental development is the general intellectual functioning below average, accompanied by significant restrictions in adaptive functioning in at least two of the following areas of skills: communication, self-care, life family, social and interpersonal skills, use of community resources, self-management, functional school skills, occupation, leisure, health and safety (American Psychiatric Association, 2000). Adaptive functioning can be influenced both by general medical conditions that may coexist with mental retardation, and by factors such as education, social and professional opportunities, social factors. In these individuals, the early application of individual psycho-pedagogical measures is required to stimulate and develop the available abilities. In addition to these measures, appropriate treatments are recommended to correct sensory (auditory or visual) and motor difficulties (Loraas, 2002).

There are multiple causes that can cause mental retardation, among which we could mention: prenatal factors (genetic abnormalities), congenital malformations or exposure of the mother - congenital infections, teratogenic agents; perinatal factors (problems due to quality of pregnancy, labor, hypoxia / asphyxia, prematurity, nuclear jaundice, cerebral hemorrhage); postnatal factors (infections, brain tumors, head trauma, lead and nitrite poisoning, other somatic diseases - severe respiratory failure, dehydration, severe hydroelectrolytic imbalances); environmental and sociocultural factors (Beirne-Smith et al., 2005, Kass et al., 2005, Harms, 2005).

Regarding the comorbidity between mental retardation and hearing loss, then things get complicated and the medical approach becomes much more complex. Early-onset hearing loss, in the period when the child's speech has not yet formed, usually determines the impossibility of speech development, unless special measures are initiated (conventional hearing aid or cochlear implant, depending on the medical indication). In cases of later onset of hearing loss at an age when the child's speech is formed, its development will continue, however retaining a number of characteristic impairments, caused by hearing loss (Wayne, 2015).

In the case of children with mental retardation, there is a delay in speech development. Many children have dyslalic speech and low vocabulary level. They understand basic speech, but more complex verbal expressions are not always accessible to them. Comorbidity with

hearing loss will cause an even more difficult language development in these children, requiring a team collaboration (psychiatrist, ENT specialist, psychologist, speech therapist), with the earliest detection of sensory deficit and, possibly, as much as possible, its correction to allow the development to the maximum capacity of these children.

Aim of the study

The research was conducted between January 2013 and December 2015 at the Institute of Psychiatry "Socola" Iași on a population of children hospitalized during the 2 years, in order to determine the share of the association between mental retardation, language disorders and hearing loss in our pediatric population.

Materials and methods

The study group of participants included in this retrospective study was selected from a number of 3,954 patients assisted in the Child Neuropsychiatry Department during that time.

We identified 276 children who presented the diagnosis of delay in mental development, and in them the association with other comorbidities (hearing loss) and the influence on language were analyzed, data that were reported in the clinical records of patients. The data were statistically processed for the stated purpose.

Results and discussion

Of the 276 children identified who were diagnosed with mental retardation (14.32%), 93 were girls and 183 were boys. When assessing the severity, most patients had a diagnosis of mild mental retardation - 156 patients compared to 87 patients with moderate retardation and 33 patients with severe mental retardation. At the analysis by age groups we observed a higher addressability in patients in the age groups 11-14 years and 8-10 years. Frequently, mental retardation is associated with autistic disorder, in which there is qualitative impairment in social interaction, impairment in communication, including delay or total lack of spoken language, various stereotypical patterns of behavior (stereotypical and repetitive motor mannerisms, persistent concern for parties of objects, non-functional rituals and others).

The analysis of the association between mental retardation and autistic disorder in the study group shows that, of the 276 patients, 51 have both mental retardation and autism. 24 of them also have language disorders (5 with mild mental retardation, 11 with moderate mental retardation and 8 with severe mental retardation).

Of the 276 children included in the study, 36.59% (101 children) have language development disorders, alalia or polymorphic dyslalia, mild to severe. We can note from the statistical analysis that with the increase in the severity of the delay in mental development increases the percentage of association with language disorders from 24% of cases in children with mild delay to 70% in children with severe mental development (figure I.1-1.1).

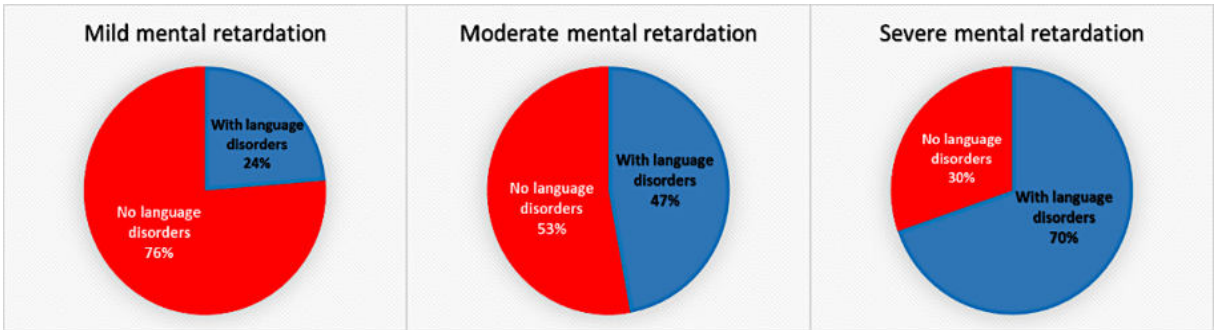


Fig. I.1-1.1. The association of delay in mental development with language disorders

- 10 children of those included in the study were diagnosed with hearing loss (6 children with mild mental retardation and 4 children with moderate mental retardation). Of these,

3 children benefited from hearing rehabilitation (two with mild mental retardation and one with moderate mental retardation).

- As mentioned above, in the case of children with mental retardation there is a delay in speech development anyway. Worldwide statistics show comorbidity with hearing impairment in about 10% of cases. In the group studied in "Socola" Institute of Psychiatry Iași, of the 276 patients, only 10 were diagnosed with hearing loss (3.62%). Of these, 3 children had hearing rehabilitation: one of the children, 4 years old, with mild mental retardation and sensorineural hearing loss with conventional hearing aid on the right ear; the second, 16 years old, with mild mental retardation, bilateral hearing aids for sensorineural hearing loss and mild form polymorphic dyslalia; the third, 8 years old, with moderate mental retardation, bilateral sensorineural hearing loss with conventional hearing aids rehabilitation and polymorphic dyslalia.

Conclusion

Children with mental retardation may have associated: hearing disorders in 10% of cases, seizures, chronic infantile encephalopathy in 30% to 60% of cases, conduct disorders, anxiety, hyperkinetic syndrome, learning or language disorders. In the case of children with mental retardation, there is, however, a delay in speech development. Many children have dyslalic speech and low vocabulary level. Comorbidity with hearing loss obviously leads to more difficult language development. It is necessary to integrate these children in special care programs, adapted to sociocultural conditions, education programs based on verbal and nonverbal communication development, social and adaptive skills. The difference between the percentage of comorbidity with hearing disorders in the studied group, of 3.62% and 10% as presented in the literature, can be given by an underdiagnosis of hearing disorders and can be an alarm signal for a closer assessment of these cases in the future.

I.1.1.2. The neonatal hearing screening – the first step of the early diagnostic and early treatment strategy

Background

The importance of deafness diagnosis in children as early as possible is already well known to both ENT specialists and neonatologists. It is proven that for children with congenital or perinatal hearing loss it is very important to be able to diagnose the form and severity of hearing loss as early as possible, so that so that appropriate treatment can be provided from the first months of life. In this case, the loss of auditory information can be minimized in a particularly important period for the maturation of the auditory system on the one hand and language acquisition and cognitive development on the other. The maturation of the auditory system after birth is achieved by myelination of the retrocochlear neural pathways and is dependent on sound stimulation, being achieved optimally when there are no auditory deficits (Moore & Linthicum, 2001, Moore et al., 1995). In case of deafness, auditory maturation is dependent on hearing restoration. Consequently, the earlier the deficiency is known and the closer the appropriate treatment is offered to the time of diagnosis, the greater the chances of achieving the expected auditory-verbal and cognitive performance.

Access to early diagnosis of deafness can only be ensured by systematically testing all children immediately after birth. Hearing loss may be favored by the presence of risk factors, but it is not necessarily conditioned by them. Thus, it is known that deafness can occur both in children with and without risk factors present, neonatal hearing testing of children with risk factors for deafness is insufficient, and can exclude from diagnosis a significant number of children, representing, according to some statistics even over 50% of the newborn population (Watkin & Baldwin, 2011).

Ensuring universal screening is a difficult task that requires the existence of a constantly organized structure over time. This structure is an interdisciplinary medical one that includes neonatologists, ENT doctors, audiologists, pediatricians and family physicians.

Auditory screening does nothing but separate newborns, based on a possible maternity test after birth, into two groups.:

- the first includes children who do not pass hearing tests, thus presenting elements suggestive of hearing loss on one or both ears and those who, although not suspected of hearing loss, have risk factors for developing hearing loss;
- the second group consists of children who pass neonatal tests on both ears and do not have any of the risk factors for hearing loss.

The target of audiological follow-up is the first group of children, who must be oriented towards specialized services in the diagnosis of hearing loss through objective tests, given the impossibility of children at this age to collaborate on hearing tests. The children in the second group are no longer followed in this program.

Main published papers in this field:

- **Sebastian Cozma**, Cristian Martu, Oana Manolache, Raluca Olariu, Gabriela Damean, Bogdan Cavaleriu, Diana Zota, Dan Martu, Luminita Radulescu. 6 years of universal neonatal hearing screening in Iași - the results of an interdisciplinary partnership. *ORL.ro*. 2015; 27(2): 26-31. ISSN 2067-6530

Scientific contributions /Clinical implications:

- Starting with 2008, I became the regional coordinator in Iași for the National Pilot Program for Newborn Hearing Screening. In this position I managed an excellent collaboration with neonatological colleagues from all maternity hospitals in Iași and with ENT colleagues, making Iași the only city in Romania where neonatal hearing screening has been carried out universally, with testing of all children throughout 10 years later. **The successful model in Iași was the basis for structuring the national screening protocol, which was started in 2019**.
- The study on neonatal screening in Iași **communicated for the first time the prevalence of congenital deafness in the newborn in Romania and the associated risk factors**.
- Together with colleagues from the Romanian Society of Audiology and Communication Pathology, which I represented as president and with patients' associations, I made efforts with the Ministry of Health that led to the start in Romania of universal neonatal hearing screening in 2019. Also, as a member of the ENT Specialty Commission of the Ministry of Health, I promoted and supported its implementation. I was a member of the commission of the Ministry of Health for the purchase of screening equipment.

Hearing loss detection program in newborns was held in Iași uninterruptedly since 2008. The success of this program was the interdisciplinary medical partnership between neonatologists, ENT doctors, audiologists, family physicians and medical administrative structures in Iași.

Aim of the research:

The study on neonatal hearing screening in Iași aims to analyze and present the results of the last 6 years, identifying the prevalence of deafness in the newborn in our area.

Materials and methods

The testing procedure was the same in all maternity hospitals, based on otoacoustic emissions. Children who fail the test of motherhood, as those who have risk factors for hearing

loss are then evaluated repeatedly in the audiology department. The aim of the current study was to analyze the results of the screening in the last 6 years. The elaboration of the protocol for conducting auditory screening in newborns was based on the guide developed by the Joint Committee on Infant Hearing in 2007 (Joint Committee on Infant Hearing, 2007) and Guidelines for Audiologic Screening - American Speech-Language-Hearing Association (American Speech-Language-Hearing Association, 1997).

The testing methodology initially included screening transient evoked otoacoustic emissions and auditory evoked potentials, tests which combined ensured, according to a study we conducted in 2008 on a group of over 360 subjects, a specificity of 98, 94% and a sensitivity of 95.18% of hearing testing (fig. I.1-1.2) (Cozma, 2008). The same conclusion was presented in numerous other studies consulted in order to develop the testing protocol (Berg et al., 2011, Johnson et al., 2005, Kirkim et al., 2008, Meier et al., 2004).

		Hearing loss		Total	Specificity	Sensibility	Positive predictive value	Negative predictive value
		YES	NO					
OEA (report S/N) TEOAE - Pass/Refer	P	7	79	86	97.58%	95.18%	98.60%	91.86%
	R	282	4	286				
Total		289	83	372				

		Hearing loss		Total	Specificity	Sensibility	Positive predictive value	Negative predictive value
		YES	NO					
ABRIS – P/R	P	8	83	91	97.17%	100.0%	100.0%	91.21%
	R	275	0	275				
Total		283	83	366				

		Hearing loss		Total	Specificity	Sensibility	Positive predictive value	Negative predictive value
		YES	NO					
OEA + ABRIS – P/R	P	3	79	82	98.94%	95.18%	98.59%	96.34%
	R	280	4	284				
Total		283	83	366				

Fig. I.1-1.2. Indicators of specificity, sensitivity, positive predictive value and negative predictive value for a group of subjects aged 0 to 10 years (n = 366)

The establishment of the testing protocol in the initial phase, in maternity, considered the international recommendations in force, but also the situation on the ground. If in the initial stage we wanted to test newborns by a mixed method that combines otoacoustic screening emissions with the auditory evoked potentials of screening for all children, later, due to the extended testing time and other factors of human and organizational nature, we concluded that testing only by otoacoustic emissions is more appropriate for our program, although according to published studies, the chances for identifying all children with hearing problems could have decreased (Granell et al. 2008). However, there are also studies on large populations of newborns that claim that there are no significant differences in screening results, regardless of which method is used: otoacoustic emissions (Akinpelu et al., 2014), auditory evoked potentials (van Dyk et al., 2015) or the combined method (both of them) (Caluraud et al., 2015, De Capua et al., 2007). An argument for preserving auditory potentials as a screening test in maternity and giving up otoacoustic emissions could be offered by reducing false positive cases and avoiding overcrowding of diagnostic services (van Dyk et al., 2015).

The process of auditory evaluation of children can take several months after birth, given that conventional hearing aids are possible after the age of 4-6 months, and cochlear

implantation after the age of 1 year. We also have a special difficulty for the therapeutic recommendation in the case of the group of children who present diagnostic elements of auditory neuropathy (Y.S. Ngo et al., 2006, Jiang, 2014).

The testing protocol was the same in all maternity hospitals in Iași from the beginning, based as a screening test on acoustic otoemissions. Children who do not pass the maternity test, as well as those with risk factors for hearing loss are then evaluated repeatedly in the audiology service. The protocol regarding the frequency of screening or diagnostic visits after the maternity testing phase (phase 0) started from the model of international recommendations, but was adapted to the particularities of the organization of medical services in Romania (fig. I.1.-1.3). An algorithm was developed to track children who needed this after birth, which included visits at 1 month, 3 months, 6 months. Due to the overcrowding of the audiology service, the one-month test phase was excluded as it was considered without benefits because no form of hearing aid rehabilitation is possible under 4 months, and serous otitis that could be diagnosed at this age cannot take the form of chronic serous otitis only after an evolution of more than 3 months. Thus, the absence of the test phase at 1 month did not prove to be an impediment in diagnosis, and the test protocol included presentation at 3 months, 6 months, and then as appropriate, until the age of 1 year. In fact, international recommendations have required adaptation to local specificities in many national screening programs (Burke at al., 2012).

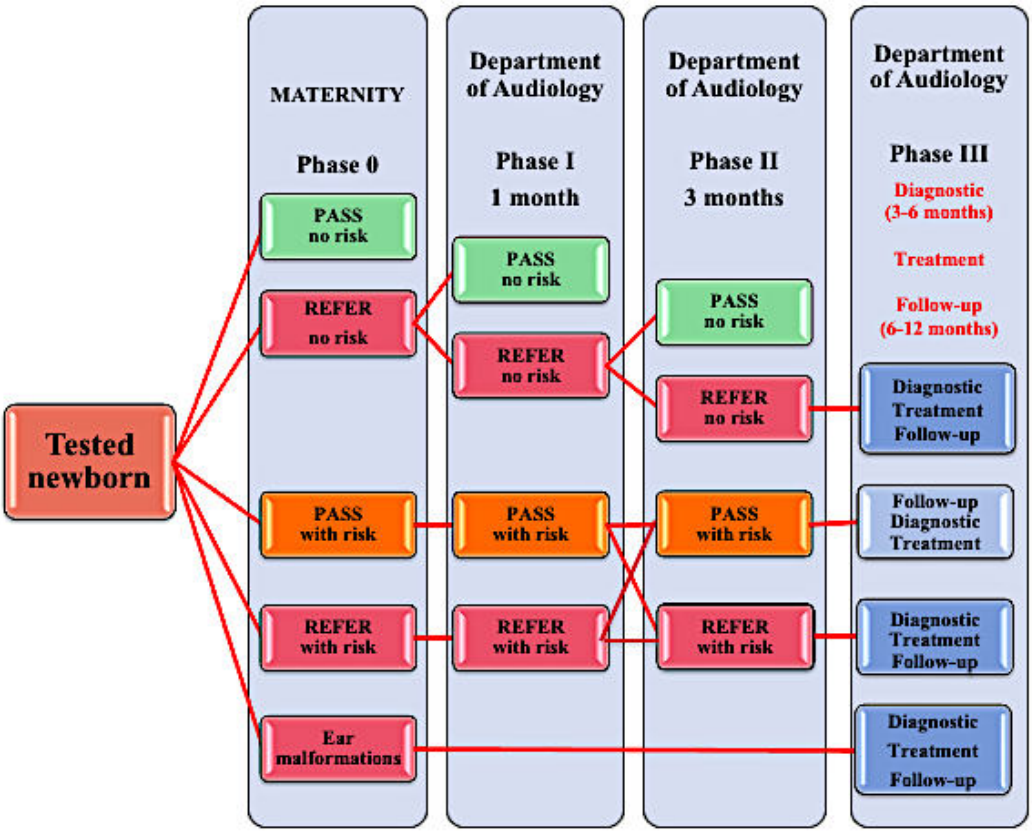


Fig. I.1-1.3. Deafness diagnostic algorithm for newborns in Iași for the period 2009 - 2014

The diagnosis of hearing loss with conventional or surgical prosthetic indication involved the repetition of the audiological assessment for the safety of the diagnosis and medical recommendation, which is necessary especially in children with postnatal maturation chances of the hearing system and those with suspected hearing neuropathy, hearing fluctuation or progressive hearing loss.

The audiological assessment in the Audiology Department for diagnostic purposes was performed with Interacoustics equipment calibrated annually and included each time: otomicroscopy, tympanometry – affirmation of the diagnosis of sensorineural hearing loss being conditioned by the presence of the tympanometric curve type A; the transient evoked otoacoustic emission (TEOAE) and/or distortion-product otoacoustic emission (DPOAE); screening test by auditory evoked potentials; Brainstem Evoked Response Audiometry (BERA); ASSR (auditory steady state response); tests to assess the child's reactions to sound stimulation in free field (Behavioral Hearing Tests) (Geal-Dor et al., 2010).

Results and discussions

In total, from January 1, 2009 to December 31, 2014, a number of 45,785 children were tested in the initial phase of maternity, representing an average of 93.45% of all births in Iași. Among the children who went through the recommended diagnostic stage after screening, an important part presented various otic medical causes that were treated with *restitutio ad integrum*.

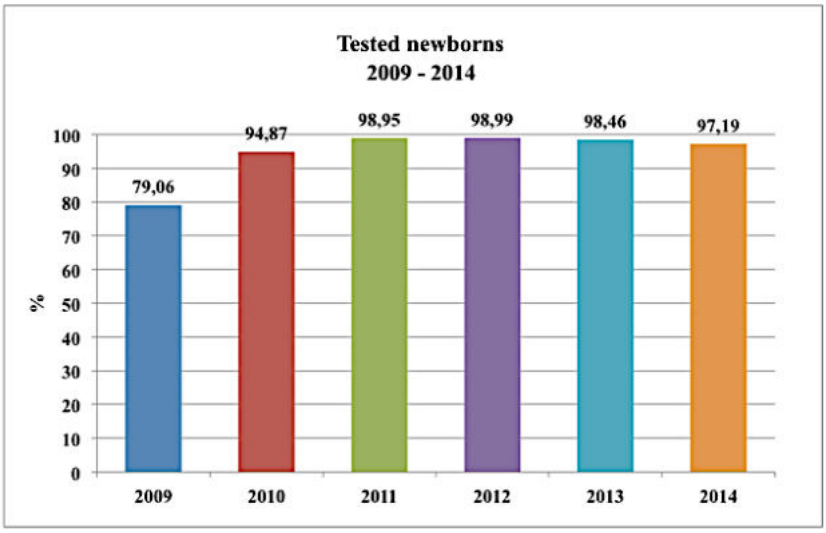


Fig. I.1-1.4. The situation of auditory testing in the newborn population in Iași for the period 2009 - 2014

Congenital sensorineural hearing loss was diagnosed in a number of 67 children in 6 years, all degrees of hearing loss being identified. Thus, our study shows that in the city of Iași the incidence of hearing loss is 1,46 per 1000 newborns. Literature data report an incidence of hearing loss in the general population of up to 3 in 1000 newborns, but most reports in Europe are around 1.5‰, a value close to our results (Vos et al., 2014, Caluraud et al., 2015).

Figure I.1-1.4 shows the situation of coverage by screening testing the population of newborns in Iași during 2009 - 2014. Except for the first year, when there were some problems in introducing the established protocol, in all the other 5 years the children were tested in a proportion of over 94.87 - 98.99%.

As a result of hearing screening, various types and degrees of deafness were identified, formulating treatment indications that were followed by the 67 children with hearing loss selected from hearing screening. Thus, 34 children were conventional hearing aids fitted, and the rehabilitation was performed at ages between 4 and 8 months. Indication of cochlear implant received 27 children from the studied population, the implantation being successful between the ages of 12 months and 24 months, depending on the associated pathology. There were also 6 cases in which the BAHA prosthesis was indicated, which was initially worn by all children on the band, the implantation being performed later (figure I.1-1.5).

Regarding risk factors for hearing loss in newborns, the database was drawn to include all children who presented the Department of Audiology for retesting or diagnosis due to the existence of at least one risk factor associated with the birth.

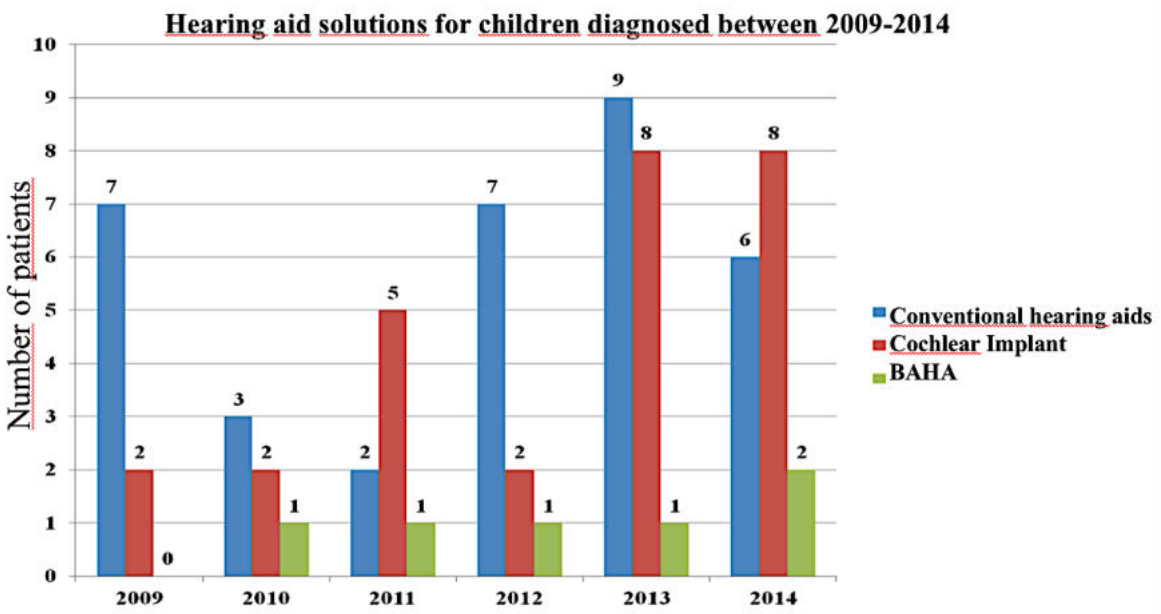


Fig. I.1-1.5. Auditory prosthetic solutions recommended for children diagnosed during screening in Iași between 2009 and 2014

According to WHO (World Health Organization) recommendations, risk factors for hearing loss include: stationary in the intensive care unit; hereditary/ family history of hearing loss during childhood; infections: cytomegalovirus, herpes, rubella, syphilis, toxoplasmosis; craniofacial anomalies; syndromes associated with hearing loss; perinatal asphyxia, low birth weight, hyperbilirubinemia; neurodegenerative diseases - Friedreich's ataxia.

As can be seen in figure I.1-1.6, in the population of newborns in Iași the most important risk factors were prematurity, hyperbilirubinemia, stationary in the intensive care unit and respiratory distress.

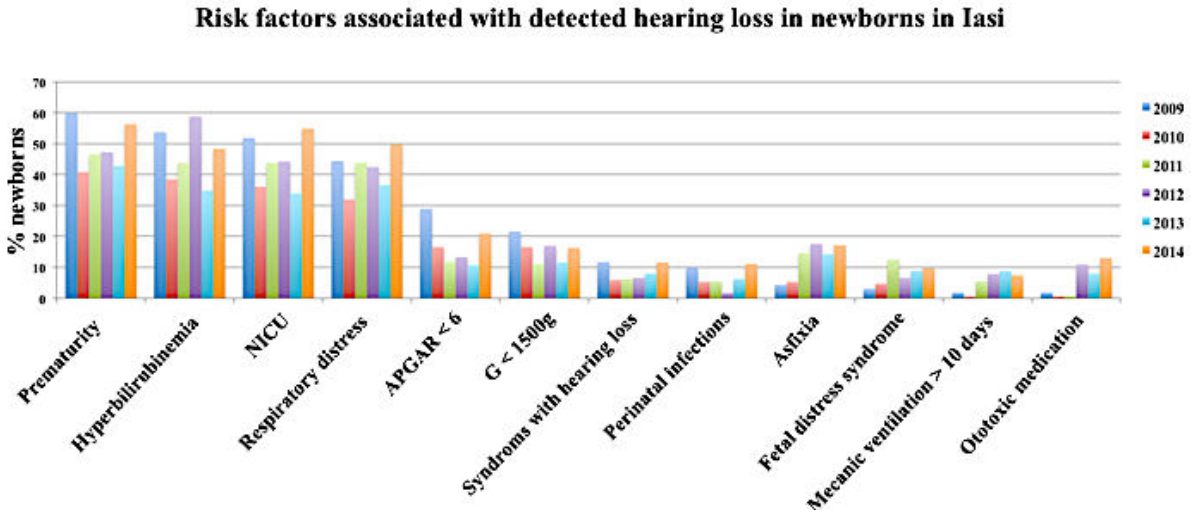


Fig. I.1-1.6. Incidence of risk factors for hearing loss in newborns from 2009 to 2014

Conclusions

The universal newborn hearing screening program, through its continuity, managed to identify in the 6 years of follow-up children who needed early treatment for hearing loss, to establish a first landmark on the prevalence of deafness in newborns, and by complementarity with the program of treatment of hearing loss through implantable prostheses, the auditory-verbal recovery of most children with early diagnosis of hearing loss was achieved. A great benfit for the health of the young child was the diagnosis and treatment, during the hearing screening and the repeated controls within it, of a significant number of children affected by a symptomatic "silent" otic pathology, acute and chronic otitis media. The strategy for development in the near future requires the creation of a new intervention in child testing, preschool and school screening, it is known that forms of hearing loss acquired after the newborn period will be discovered late in children in the absence of regular screening. Multiple publications claim that over 50% of children who are diagnosed with hearing loss in preschool and school screening are among those who have passed post-birth screening tests (Watkin & Baldwin, 2011).

Contribution:

A very important product with significant clinical utility is universal newborn hearing screening protocol, to which our studies and experience have substantially contributed, together with that of colleagues from other university centers, is shown below:

Universal screening involves hearing testing of all newborns on both ears, regardless of the presence or absence of risk factors for hearing loss.

How?

The testing will be performed by transient acoustic otoemissions - screening test. The test will be repeated if the recording conditions are not the recommended ones (artifacts below 20% and probe stability above 80%).

The result will be PASS or REFER, and the recommendations for maternity discharge will take into account:

- the result of the test on each ear;
- child category (with or without risk factors);
- compliance with the national test protocol below.

When?

- one day before discharge (day 2-3 in healthy newborns; one day before discharge for newborns staying longer in maternity);
- in case of a REFER result to at least one of the ears, it is recommended to repeat the test to confirm the result before discharge.

Results and follow-up:

- **healthy newborns who obtained PASS in both ears at the first test** - monitoring language development by parents; audiogram before attending kindergarten and school;
- **healthy newborns who obtained REFER in at least one of the ears at the first test -** retest in the maternity ward before one month of age;
- **healthy newborns who obtained REFER to at least one of the ears at the second test** - audiological diagnosis in a specialized Audiology / ENT center at the age of 3 months;
- **newborns in intensive care units (ICU) in maternity wards or pediatric wards who obtained PASS in both ears** - audiological evaluation at 6 and 18 months, in specialized Audiology / ENT centers;
- **newborns in intensive care units (ICU) in maternity wards or pediatric wards who have obtained REFER in at least one of the ears -** audiological diagnosis in a specialized Audiology / ENT center over 3 months (no later than the age of 6 months);

For those who have been denied the suspicion of hearing loss, the development of language by parents will be pursued; audiogram before attending kindergarten and school;

- **newborns diagnosed with hearing loss following the audiological diagnosis from specialized Audiology / ENT centers -** hearing prosthesis recommendation; evaluation of the benefit of prosthesis at 3-6 months.

Families of newborns who obtain a REFER to at least one of their ears at the hearing screening test (first or second test) in maternity hospitals must be notified for the next stage - mother family doctor / mother phone call / specialized Audiology / ENT center programming. Within a specialized center, the follow-up strategy will be established after 18 months, depending on the case.

I.1.1.3. The genetic screening of the deaf child - ethical considerations

Background

The technological progress in the last couple of years has provided a high standard for the treatment of different diseases. As well, the DNA decoding created the possibility for prenatal diagnosis in different diseases like deafness, through the identification of the mutation gene responsible for hearing impairment, among which the partial or total loss of hearing (Abe et al., 2007; Hone & Smith, 2003; Schade et al., 2003; Sugata et al., 2002; Toader, 2010). Genetic mutations are encountered in 60% of the congenital deafness. Molecular diagnosis of deafness in families with hearing impaired children could predict the probability of a mutation to be transmitted to other members of the affected family, being the reference point for genetic counseling and, eventually, for the prenatal diagnosis of deafness, at parents request (Coviello et al., 2004; Marpeau, 2008). This approach opens a real possibility for deafness eradication. In some countries, molecular diagnosis is a matter of daily routine in establishing the etiology of deafness this being the third direction of development.

Genetic mechanisms appear to be involved also in the pathogenesis of deafness caused by middle ear inflammatory diseases. Pediatric cholesteatomas are usually more aggressive and invasive and studies have demonstrated that genes who were important for inflammation (for example, KRT6B, SPP1 and S100A7A) are highly up regulated in cholesteatoma compared to external auditory skin. However, it is yet unclear whether this altered control is due to defects in the mechanisms and underlying genes that control proliferation, or to cytokines released from infiltrating inflammatory cells (Maniuet al., 2014). The A1555G mutation in the mitochondrial small ribosomal RNA gene has been associated with aminoglycoside induced hearing loss (Moroti Constantinescu et al., 2009).

Main published papers in this field:

- Luminița Rădulescu, Cristian Mârțu, Tudor Rădulescu, Lucia Corina Dima-Cozma, Oana Bitere, Corina Butnaru, Horațiu Ștefănescu, **Sebastian Cozma**. Genetic screening of deaf children: ethical considerations. *Review of Research and Social Intervention.* 2018; 60: 180-187. (IF=1,076)

Scientific contributions /Clinical implications:

- Genetic screening for hearing loss is not yet widely applied clinically, sparking international debate on ethical issues and clinical implementation models. This issue is very actual in our society, in recent years the cochlear implant being an increasingly recommended solution.

Aim of the research

The paper discusses the ethical problems linked to the use of genetic screening in the diagnosis of the hearing loss. To forbid or determine (at request) the birth of a deaf child, to consider deafness to be a culture or a disability, to require the informed agreement for genetic screening are the ethical dilemmas approached in this paper; it is also an analysis of these facts from the point of view of the deaf community and of the people with normal sense of hearing. The present paper would like to open a debate concerning the recent opportunities which have made possible the early genetic diagnosis and the treatment of deafness with the cochlear implant, the use of cochlear implant leading to the eradication of deafness (as a disability) and therefore, to the disappearance of the deaf culture.

Discussions:

Nowadays, we are dealing with an ethical challenge in the genetic management of deafness. In the context of molecular screening of hearing loss some questions arise:

- Is it ethical to forbid the birth of a deaf child?
- Can we integrate deafness into a culture or should we consider it to be a disability?
- Is it ethical to use genetic information regarding the birth of a child according to his/her hearing condition? It is well known that there are deaf people who have the desire to give birth to a deaf child.
- Is the cultural identity of deaf people in danger of disappearing?
- Is it necessary to have the informed consent for molecular diagnosis of deafness?

Having diversity in view, one can ask if deafness has any advantages. It is known, for example, that sickle cell anemia provides some resistance to malaria. It is also a fact that people with Down syndrome are protected from some forms of cancer (Hasle, Clemmensen & Mikkelsen, 2000).

Can we integrate deafness into a culture or should we consider it to be a disability? Authors like Johnson T. (Johnson, 2004; Johnston & Schembri, 2007) supported the view that deafness is not a disability. Those who support the deaf culture say that deafness unlike other disabilities has its own language – the sign language – therefore creating, in its turn, a linguistic community. Having this in view, deafness is not a disability (Johnson, 2004; Johnston & Schembri, 2007; Padden & Humphries, 1988). In 2001, in a research conducted by the Study Center of Deafness in Bristol it is shown that the majority of deaf persons consider deafness as a disability (Dye, Kyle, Allsop, Dury & Richter, 2001).

If we could choose between being deaf or having the sense of hearing, what would be our option? The advantage of being able to hear or the lack of this capacity? The study made in Bristol certify that this conclusion is valid for a large number of deaf people. Asking a deaf person "Would you rather hear?" has no sense and could not have any answer. It is not possible to limit deafness to the absence of only one sense. A deaf person cannot imagine being something he has never experienced.

Is it ethical to intend to have or to determine the birth of a child who will be deaf?

If deafness is considered not to be a disability, then there are no ethical problems for the person who wants to have a deaf child. But, as the majority of people consider deafness to be a disability, an ethical dilemma might arise. In Nazi Germany deaf persons were not allowed to get married, such persons were forced to be sterilized or were even killed (Schuchman, 2004).

Advantages and limitations of deafness genetic screening

Today the situation is totally different, hearing loss screening and early treatment make it possible for a person to be able to hear. Bioethics studies evaluated the moral values and concepts to be included in the decision making. In a complex and variegated moral universe a minimum just and necessary moral code should secure the maximum of personal happiness for everyone. In the universal minimum we should include the principles of not harming someone, of being good to someone (the principle of beneficence), the principle of justice and the

principle of autonomy. It is to be understood that each parent wants what is the best for his child. Therefore, a parent cannot desire (according to the principle of beneficence for his child) to give birth to a child with a predictable but avoidable disability.

If the parents do not perceive deafness as a disability, then their desire to have deaf children is to be understood (Murray, 2004). If we accept that deafness is not a disability the position held by such parents can be ethical. On the other hand, it is not necessary to create deaf children just to perpetuate the culture and language of the deaf people.

Have parents the right to select their children according pro and con deafness? The human biologic right implies to have five intact and functional senses at birth. With this requirement, the conception of a child with limited sensorial capacities is a violation of this human biologic right.

The right to have an open future, for as much as it is possible (an open future means not to limit or confine in any way the life endowment) is in opposition with the development potential of the child who starts in life from the very beginning with a disability. A deaf child with deaf parents can discover in his past the following: parents knew that their child might be deaf but did not take either the hearing loss or the genetic screening and/or reproductive screening for diagnose and early treatment of deafness; parents take the hearing loss screening but do nothing so that their child should not to be deaf; parents use genetic techniques to be sure that their child will be deaf.

Is it ethical to use genetic tests and reproductive techniques to decide the birth of a child according to his auditory status? The knowledge and techniques in the field of genetics have made rapid progress and the information provided by mass media has promoted the opportunities in this domain (Toader, 2010). In 2000, Brugner (Brugner, Murray, O'Riordan, Mathews, Smith & Robin, 2000) in a study conducted in the USA, shows that 87% persons are willing to have genetic prenatal tests; Martinez in a study from 2003 indicates a percentage of 64% (Martinez, Linden, Schimmenti & Palmer, 2003), Middleton indicates that 28% of the deaf people are willing to have prenatal genetic tests (Middleton, 2004).

In many cultures, societies or religions the use of such a technique is justified from a medical and ethical point of view. In some other areas, abortion is not allowed; in such cases for couples at risk a solution could be the selection of germinal cells to create an embryo without disabilities. Religion is a major component of human communities and was involved in providing recommendations on various modern treatments, maintaining a preferable dialogue with medicine and patients (Dima-Cozma & Cozma, 2012).

From the point of view of the legal foundation, the molecular screening of hearing loss may be based on Article 34, 1st paragraph of the Constitution, which states that the "Right to defend health is guaranteed" and on the 2nd paragraph where it is stipulated that: "The state is obliged to take measures in order to insure the population's hygiene and health". The molecular diagnosis in a child is possible only after having the agreement of the legal tutor and only if the screening is made for the benefit of the child or if the result of the test offers the identification of the predisposition to a certain disease for the tested child or for his future siblings.

In the Additional Protocol of the Convention for the Human Rights and the Dignity of the Human Being the genetic tests made for the sake of research in the field of biology and medicine are ruled out.

Conclusions

The genetic screening should be in accordance with the objectives of the National Program, which coincides with our aims and those in "The Principles of the Patients' Rights in Europe", which have been internalized through the adoption of the Law number 46 from 2003 regarding the patient's rights, among which, it is recognized the right "for medical assistance of the highest quality". The clinical use of the genetic screening is not at all far away, since there are already centers that provide this assessment.

I.1.2. The contribution of the objective tests for the assessment of the hearing

Introduction

Hearing loss is a sensory disorder that needs to be diagnosed early in life to provide these children proper developmental conditions (Fulcher et al., 2012). Diagnosis requires a battery of tests including objective hearing assessments, such as auditory brain stem responses (ABR) and auditory steady-state responses (ASSR), which set hearing thresholds in young children. However, in young children, collaboration with these tests is more difficult. The electrophysiological tests require the child to be as quiet and motionless as possible, to reduce the myogenic activity that may interfere with the recordings of the auditory evoked potentials (Pillion et al., 2010). Tests can be done either in spontaneous sleep, especially in young children, in induced sleep, with the help of drugs, or under general anaesthesia (Atkin et al., 2005). The latter is not without risks in very young and young children, it can be traumatic for children and parents, and the costs of the procedure and the time spent in the operating room are not to be neglected. Therefore, tests in natural sleep or in induced sleep are desirable alternatives.

I.1.2.1. The sedation of paediatric patient – a condition for objective hearing tests?

Sedation with drugs is a method commonly used in electrophysiological assessment (ABR and ASSR) of hearing in young children. It aims to reduce physical and mental discomfort, to reduce anxiety and, in particular, in case of ABR responses, to reduce unwanted movements that could influence the results (Cote et al., 2006). The major advantage of sedation is that it can also be performed outside of the operating room (Zempsky et al., 2004).

The audiological assessment for small children depend often of sedative drugs that can be administered orally, nasally, intravenously, intramuscularly, subcutaneously, or by inhalation (Keira, 2013). Of these, the most commonly used in paediatric sedation are a mixture of nitrous oxide and oxygen, administered by inhalation; or midazolam, a benzodiazepine, administered by the intramuscular, intravenous, oral, rectal, sublingual, or nasal route. Ketamine can be administered intravenously or intramuscularly; propofol is administered intravenously; and sevoflurane can be administered via inhalation or intravenously. Fentanyl can be administered parenterally, transdermally, nasally, or orally. Sufentanil, chloral hydrate, can be administered orally or intrarectally, with more sedative and less analgaesic effect. Hydroxyzine and promethazine, administered orally or intramuscularly, are often associated with chloral hydrate, pentobarbital, metohexital, or thiopental. Barbiturates are administered orally or rectally. Melatonin is administered orally. Dexmedetomidine, an imidazole compound, can be administered intravenously or nasally (Attri et al., 2017).

Regardless of the type of sedative used, adverse effects may occur (Cote et al., 2000), the most common being vomiting (55.5%), agitation (17.9%), hypoxia (14.8%), and apnoea (7.1%) (Bellolio et al., 2016).

The type of sedative and route of administration are chosen depending on the child, on the type of procedure, and on the desired effect. If the procedure is not painful and it requires only a patient's immobilisation, simple sedation can be used, preferably non-parenteral, such as chloral hydrate, promethazine, midazolam, melatonin, or barbiturates (e.g., pentobarbital, methohexital, thiopental, or dexmedetomidine) (Fallah et al., 2015).

Main published papers in this field:

- Violeta Necula, Mirela Cristina Stamate, Cristina Blebea, **Sebastian Cozma**. Safety and effectiveness of chloral hydrate in outpatient paediatric sedation for objective hearing tests. *International Journal of Pediatric Otorhinolaryngology.* 2019*;* 126. 109605. (IF=1,225)

Scientific contributions /Clinical implications:

- Our research shows that the objective audiological assessment for children can be done very efficient avoiding the general anesthesia and also saving time and money for surgery room, having in the same time a quite, calm baby patient using the chloral hydrate.

Introduction

Chloral hydrate was discovered in the 19th century and was used primarily until barbiturates and benzodiazepines displaced it. It is administered both orally and rectally and is rapidly absorbed into the gastrointestinal tract, then metabolised by alcohol dehydrogenase in the liver and erythrocytes, in trichlorethanol and trichloroacetic acid, the active metabolites (Gauillard et al., 2002). Chloral hydrate is an easy to administer sedative with a high success rate and a low prevalence of adverse effects, unlike other traditional sedative agents that may have more sig- nificant respiratory or cardiovascular adverse effects (Wheeler et al., 2001, Malviya et al., 2004). Some of the adverse effects are abdominal distension, vertigo, ataxia, headache, paradoxical agitation, cancer (in case of prolonged use), hallucinations, nightmares, seizures, vomiting, hypotension, unpleasant taste, and cardiac arrhythmia (Martindale, 2014).

The adverse effects most commonly reported in the literature were in very young children, less than 6 months of age, including apnoea, desaturation, hypotension, vomiting, and prolonged sedation (Heistein et al., 2006). Chloral hydrate is recommended in painless procedures in children who cannot cooperate; for neurophysiologic diagnostic procedures, such as ABR; electroencephalography; electrocardiography; imaging evaluations; ophthalmologic manoeuvers; and in some procedures in cardiovascular intensive therapy (Abulebda et al., 2017, Hassanzadeh, Aminzadeh, 2016, West et al., 2013, Chen et al., 2017).

Aim of the research

The purpose of this study was to evaluate incidents and adverse effects arising from the administration of chloral hydrate. The safe administration of chloral hydrate allows the testing of children in the outpatient department, relieving the hospital of a series of costs involving general anaesthesia and hospital admission.

Material and methods

The study was conducted between July 2014 and April 2018, and it was approved by the Ethics Committee of the University of Medicine and Pharmacy and by the Ethics Committee of the hospital, in compliance with the Declaration of Helsinki. Informed consent was obtained from every family to use the child's data.

The group consisted of 323 children who required sedation with chloral hydrate to perform objective hearing tests with ABR and ASSR, with the purpose of establishing an audiological diagnosis.

The study group included children between 5 months and 7 years of age requiring sedation with chloral hydrate to perform electrophysiological auditory tests. In children less than 1 year of age, the testing was performed during natural sleep, with a few exceptions. Older children, over the age of 4–5 years, were sedated only in cases in which they would not

cooperate for behavioural assessment or when they did not sit quietly to be tested for ABR and ASSR, usually in the case of neuropsychiatric disorders. Children who could be tested in natural sleep and did not require sedation were excluded from this study. Prior to the procedure the child was evaluated by the otolaryngologist. The assessment included health history, allergies, other diagnostic tests, airway assessment, previous sedation and/or analgesia and anaesthesia history, and other relevant details. In medically complex cases an anaesthesiologist was asked to evaluate the patient (ASA, 2014).

After a consultation with an Ear, Nose, and Throat (ENT) specialist, the chloral hydrate was administered by a trained nurse, by the oral route, in a dose of 50–100 mg/kg body weight, without exceeding the total dose of 2.5 g (Mace et al., 2008). In the case of vomiting, depending on the amount administered, the dose was further supplemented. Also, if sedation was not obtained after 45–60 min, the dose was supplemented by 20–40 mg/kg body weight. After the sedative was administered, the child was placed in a quiet and soundproofed room, together with the parent, to fall asleep, under the supervision of the nurse. During the sleep, the children were monitored with a pulse oximeter and the reading of dates was at every 10 min. After sleep onset, surface electrodes were placed. According to our protocol, we started with the tympanogram and otoacoustic emissions after which the auditory evoked potentials and the ASSR were performed. After completion of the testing, the child was stimulated to wake up. Children who did not wake up immediately after the completion of the testing were further monitored until they woke up, and all of them remained at the hospital until awake.

The collected data were processed with the Statistical Package for Social Science (SPSS Statistics 21.0) program.

Results

The group was made up of 323 children aged between 5 and 83 months (7 years old), the average age being 28.18 ± 18.10 months, a median of 26 months [95% confidence interval (CI); 26.20–30.16). In the studied group, 26% were children between 5 months and 1 year of age; 58.8% were between 1 year and 4 years of age; and 15.2% were older than 4 years of age.

The group of children were 40.2% girls and 59.8% boys; 43.3% were from rural areas, and 56.7% were from urban areas.

In the studied group, 50.5% of the patients did not have other known associated conditions. Of 323 tested children, 21 were diagnosed with various syndromes such Bartter (2), BOR (1), Down (5), Treacher-Collins (5), Goldenhar (4), Hunter (2), West (1) and Wolf-Hirschorn (1). 24 children had craniofacial dysmorphism: five had Treacher-Collins features, five had cleft palates, four had craniofacial malformations without any known syndrome and ten children had unilateral auricular malformation. Four of those with unilateral auricular malformation had Goldenhar syndrome, the rest did not have any other syndrome features. 56 (17.3%) children were tested because of premature birth and because they did not pass the screening. 41 (12.7%) children presented with neuropsychiatric conditions such as autism spectrum disorders and attention deficit/hyperactivity disorder. Eight (2.5%) children had cardiac malformations and three had kidney malformations. Two children were diagnosed with CMV intrauterine infection, one child had a history of encephalitis, one had hydrocephalus and one had tetraparesis.

Of all tested children, 118 (36.5%) had normal hearing; the rest had unilateral (4.3%) or bilateral (10.3%) conductive hearing loss, unilateral (1.5%) or bilateral (44.2%) sensor- ineural hearing loss, or mixed hearing loss (3.2%). The dose of chloral hydrate administered ranged from 0.50 to 0.83 mL/kg body weight, with an average of 0.75 mL kg body weight [95%CI: 0.74–0.75, standard deviation (SD) = 0.52].

Sleep onset occurred within 10–75 min of administration. The success rate, defined as children who fell asleep and slept during the entire testing, was 94.1%. Inadequate sedation ranged between 3.6% and 6.1% but also with no statistical differences. When compared, rates

of sedation failure were significantly different between the group of children between 1 and 4 years and the group of children older than 4 years, p = .046.(fig. I.1-2.1).

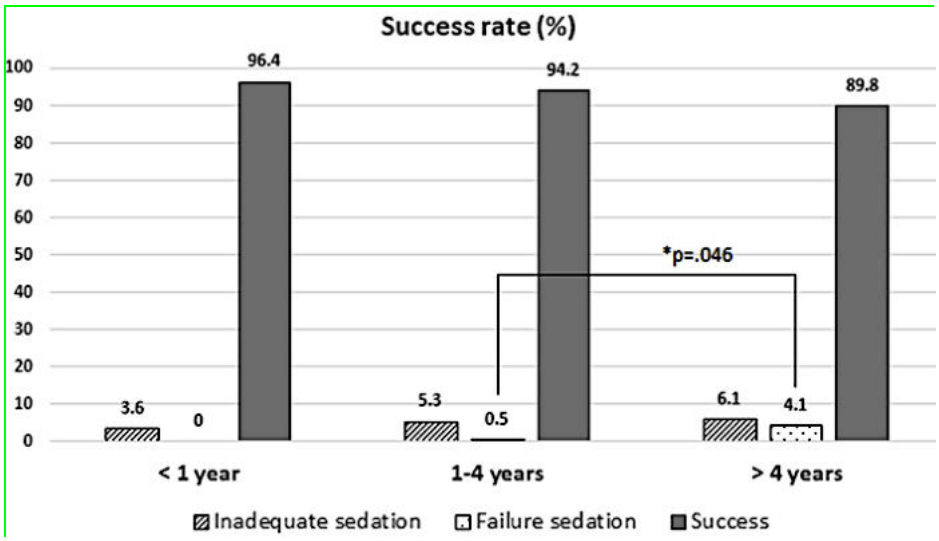


Fig. I.1-2.1. The success rate was greater than 94% in children under the age of 4 years, and slightly less than 90% in children older than 4 years of age. There was no statistically significant difference between the age groups either in the success rate or the rate of inadequate sedation. As for the failure rate, the difference between the 1–4 years age group and the over 4 group had statistical significance, p = .046

There were only three children (0.9%) who did not fall asleep even after the initial dose of chloral hydrate was supplemented by 20–40 mg/kg body weight. These children were subsequently tested with chloral hydrate, in one case (0.3%) and, in two cases, under general anaesthesia (0.6%).

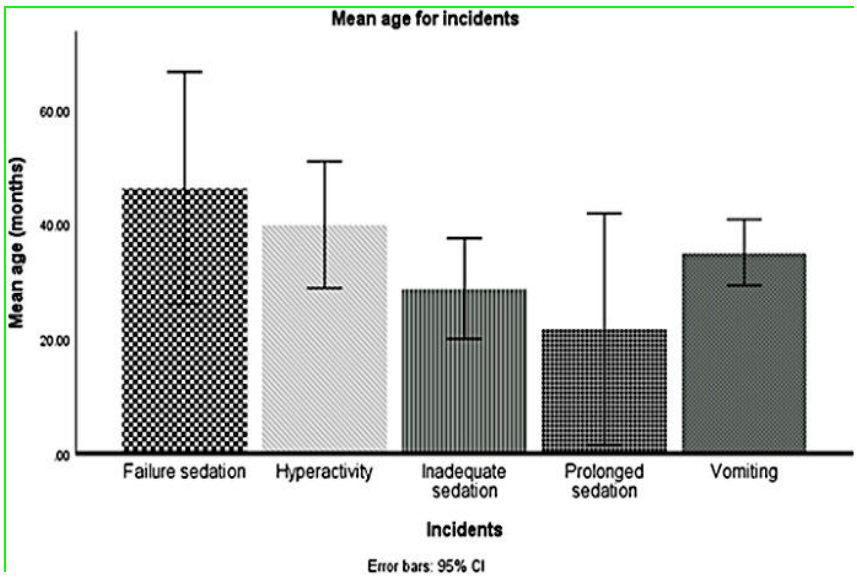


Fig. I.1-2.2. The mean age of children for each incident and complication that occurred after the administration of chloral hydrate and the 95% confidence interval. Hyperactivity and sedation failure were more often in older children and the mean age in the study group was between 3 and 4 years. Vomiting was often around the age of 3 years while prolonged sedation occurred in younger children, about the age of 2

Several children woke up during testing (5.0%) before the completion of the protocol and required supple- mentation of the chloral hydrate dose, or were rescheduled for testing. These children were either left quiet to fall asleep again, or the solution dose was supplemented.

Vomiting was more commonly seen in older children and in those who did not respect the time interval between the last meal and the drug administration. Some children (3.1%) experienced a state of agitation after administration of the solution, and sleep onset was slower; however, no changes in cardio-respiratory parameters were noted (figures I.1-2.2. and I.1-2.3.). Patients were monitored with the pulse oximeter during testing, and O2 saturation did not decrease to below 95%; the pulse was within normal limits for all children. No patient required oxygen administration or other manoeuvres to maintain cardio-respiratory functions.

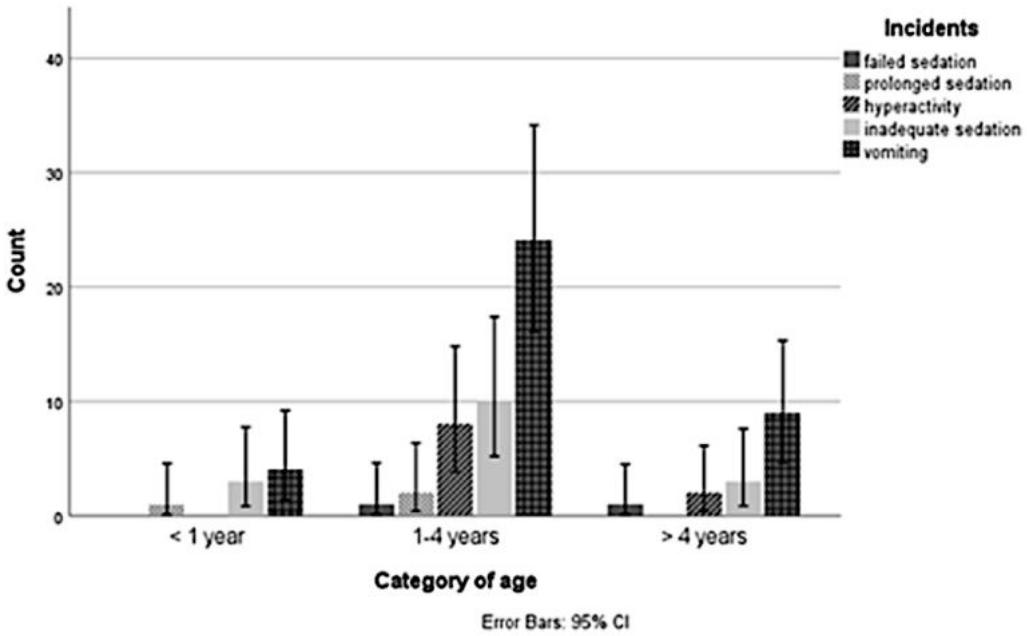


Fig. I.1-2.3. Adverse effects, by age group, and their incidence. In every group, vomiting was the primary side effect, followed by inadequate sedation and hyperactivity

The test duration varied between 45 and 100 min. Most patients woke up immediately after the testing, upon the removal of electrodes. Others woke up after 10–30 min. In the studied group, only three (0.9%) patients experienced prolonged sleep (more than 4 h after the first drug administration), but without cardio-respiratory changes. Those patients remained in the hospital until the next day, were monitored, and subsequently discharged without further complications (figures I.1-2.2. and I.1-2.3).

Discussions

Objective hearing assessment in young children is extremely important for establishing an early diagnosis. To assess hearing and determine neurophysiological hearing thresholds, it is necessary to perform the ABR and the ASSR, which require a quiet, preferably sleeping patient, to minimise artifacts. The investigation can be done either in natural sleep or in drug-induced sleep or under general anaesthesia. Each method has its advantages and disadvantages both in terms of time and cost. The mean dose of chloral hydrate was 75 mg/kg and, in some cases, it was necessary to supplement it by 20–40 mg/kg to obtain the proper sedation. The success rate was 94.1% with a single dose of chloral hydrate and 99.1% if we consider the cases that required dose supplementation. The value obtained by us was similar to that reported by Avlonitou et al., of 99.7% (Avlonitou et al., 2011), whereas West et al. (West et al., 2013) reported a success rate of 92.79% in a group of 1509 sedations at a single dose of 80 mg/kg and 96.69% when a top-up dose was used. Studies in which lower doses were used, 50–75 mg/kg,

reported lower success rates, ranging from 64% to 89.4% (Keidan et al., 2004, Lee, 2012, Marti-Bonmati, 1995). There were no incidents or major complications in the studied group. The most frequent incident was vomiting, followed by inappropriate sedation and hyperactivity.

In a systematic review and meta-analysis of the incidence of adverse effects due to child sedation procedures in the emergency department, Bellolio et al. (2016) noticed that the most commonly reported adverse effect was vomiting, followed by agitation, hypoxia, and apnoea. Vomiting had a higher incidence in studies in which sedation was done with ketamine (80.7 per 1000 sedations), whereas agitation was more common in studies with midazolam. Hypoxia has been reported more often in the studies with etomidate, and apnoea has been associated particularly with propofol (Bellolio et al., 2016).

Vomiting was more common in our group than in other studies (11.5%). West et al. (2013), in a study conducted on 1509 sedations, reported a lower incidence of vomiting, 0.53% (West et al., 2013) compared with other studies in which the incidence was higher. In the study conducted by Lee et al. (2018) in a group of 1590 patients, the incidence of vomiting was 6.5% (Lee et al., 2018). In a study reported by Avlonitou et al. (2011), the incidence was 11.4, similar to what we noticed (Avlonitou et al., 2011).

In our study, the second most common adverse effect was inadequate sedation. Of the 323 children, 16 (5%) woke up during the testing and required dose supplementation or rescheduling. West et al. (2013) reported inadequate sedation in 7.2% of children, at a dose of 80 mg/kg of chloral hydrate, with dose supplementation by 40 mg/kg (West et al., 2013). In another study, Abulebda et al. (2017) reported, in a group of 73 children, 14% of children required supplementation of the initial dose of chloral hydrate of 33.4 mg/kg (Abulebda et al., 2017). In their study, Avlonitou et al. (2011) reported an initial dose of 40 mg/kg of chloral hydrate, with additional 40 mg/kg for those who required it. The success rate after the first dose was 72% for children older than six months and 100% for those younger than six months; and only 5 (0.3%) could not be sedated with chloral hydrate (Avlonitou et al., 2011). In a group of 148 children, Hijazi et al. (2005) reported a success rate which increased from 79% to 95%, with the initial average dose of chloral hydrate being 56.9 ± 9.3 mg/kg and a second dose of 18.5 ± 6.4 mg/kg (Hijazi et al., 2005).

Agitation or hyperactivity after administration of the chloral hydrate occurred in 3.1% of cases. In the study conducted by Avlonitou et al. (2011), the percentage was 8% (Avlonitou et al., 2011), whereas in the study conducted by Wandalsen et al. (2016), the percentage was just 1.3% (Wandalsen et al., 2016). As in the study reported by West et al. (West et al., 2013) the incidence in our group was between the two values, close to that reported by Valenzuela et al. (2016), of 5% (Valenzuela et al., 2016). As a matter of fact, agitation is a complication found with other types of sedatives, as shown by the review performed by Bellolio et al. (2016), in which agitation was reported in 18.2 of 1000 cases. Studies with midazolam report the highest incidence of agitation (Bellolio et al., 2016).

Prolonged sedation occurred in three patients (0.9%) in our study, whereas Wandalsen et al. (2016) reported 0.4% of cases with prolonged sedation (Wandalsen et al., 2016) and 1.33% was reported in the study reported by West et al. (West et al., 2013). Eleven cases required only supervision, without any other in- terventions, and the children were hospitalised overnight, without complications. No greater incidence of adverse effects was observed in patients with cardiac malformations, and there were no cases of anoxia, bradycardia, or other majour adverse effects in our study. The data are consistent with other studies in which chloral hydrate was administered to cardiac patients without majour adverse effects (Chen et al., 2017, Ratnapalan, 2014). The limitations of the study are due to the lack of a standardised protocol for the administration of chloral hydrate as well as the limited monitoring possibilities of patients in an outpatient setting. The majour advantage of chloral hydrate in audiology, unlike many other

substances, is the duration of sedation, which allows performing painless tests that can last more than an hour.

Conclusions

Our study confirms what studies have shown in recent years about chloral hydrate, that sporadically administered, without exceeding the permissible doses, adverse effects are not more common or more severe than in the case of other substances used for sedation. Like any substance administered, it has its advantages and disadvantages, and the use of chloral hydrate should be done judiciously, in appropriate conditions, by observing the doses to achieve effective and risk-free sedation. Besides the low costs, the big advantage is that it can be administered outside the operating room but under specialised supervision.

I.1.2.2. The validation of auditory steady state response as a reliable tool for hearing loss diagnostic

Introduction

Auditory Steady State Response (ASSR) is a modern audiological test used for the multifrequential evaluation of auditive tonal thresholds, permitting plotting of a valid audiogram for patients who cannot or do not want to participate to classical audiometric tests (tonal audiometry), or for those incapables of doing such things (babies, comatose patients, simulants). The test is extremely important for recommending cochlear implant in children. It requires and the relaxation or sleep condition it assumes.

The auditory thresholds is are extremely important in the recommendation and adaptation of hearing aids for babies or little children, as an early intervention may assure a good auditive and verbal performance.

Main published papers in this field:

- C. Mârțu, Oana Manolache, D. Rusu, Raluca Olariu, **S. Cozma**. Validation of the ASSR test through complementary audiologyical methods. *International Journal of Medical Dentistry.* 2011; 1(3): 226-231.

Scientific contributions /Clinical implications:

- The study was published at a time when ASSR was in its infancy as a reference test for hearing thresholds and was yet another piece of evidence in favor of widespread clinical use. The results were presented at the World Congress of Audiology in Moscow, Russia, 2012 where they were highly appreciated by some of the most prestigious specialists in the field.

Aim of research

The objective of the study was to validate the audiometric profile and the auditive thresholds obtained through ASSR, by comparative analysis with the subjective auditive thresholds obtained by tonal liminal audiometry in both children and adults.

Materials and methods

The patients were evaluated first by otomicroscopy and tympanometry in the Department of Audiology and Vestibulogy of the Clinical Recovery Hospital of Iaşi. We selected patients with normal hearing and also with hearing loss, all with normal otomicroscopy and normal tympanometry and we excluded patients with middle otites or malformative anomalies. We included 7 patients able to cooperate to pure tone audiometry, which means 14 units of study (14 ears).

The study protocol, included the pure tone audiometry, followed by the record of the estimative audiogram by ASSR, both in a standard sound-proof room. ASSR was performed with the patient in decubitus position, as the test is a long-time one (2 hours, on average), thus requiring a corresponding muscular relaxation. The pure tone audiometry (PTA) were made with an AudioTraveller AA222-type audiometer produced by Interacoustics, using the descending testing method. Of interest were only the tonal thresholds in air conduction, if considering their subsequent comparison with the thresholds estimated by ASSR (also obtained by air stimulation). ASSR determinations were performed on the Eclipse (auditory evoked potentials system) produced by Interacoustics. Following the explanations given to the patient, the skin was cleaned with an abrasive conducting cream and 4 contact electrodes were mounted on the scalp, according to an ipsilateral FPZ – mastoide procedure. The tone-burst stimuli applied were presented by insert ear phones, at an initiation intensity of 65 dB HL. In a subsequent study, the stimulation intensity was either decreased or increased, from one case to another, up to the determination of thresholds on each frequency, while border intensity was checked twice, both for the accepted and the rejected stimulus. The curves were registered with a waiting time of 5 to 15 min on each frequency and intensity, which prolonged to a considerable extent the test time, while increasing significantly the quality and precision of the test. The recordings were analyzed and subsequently processed with the Excel program.

Results and discussions

The observation made during the ASSR tests was that the duration of recordings was shorter for mean and high frequencies and longer, respectively, for low frequencies, the testing time for each curve becoming longer and longer as the stimulation intensity gets close to the auditive threshold. The mean time given to each patient included in the study exceeded 2 hours. The age of the patients ranged between 6 and 60 years.

Four subjects presented liminal tonal auditive thresholds (ATL/PTA) characteristic to normal hearing, while 3 of the tested patients suffered by hear loss.

The individual results of the study are presented by comparative graphical representation of the auditive thresholds obtained by the two methods, the subjective one, i.e. the tonal liminal audiogram, and the objective one, ASSR.

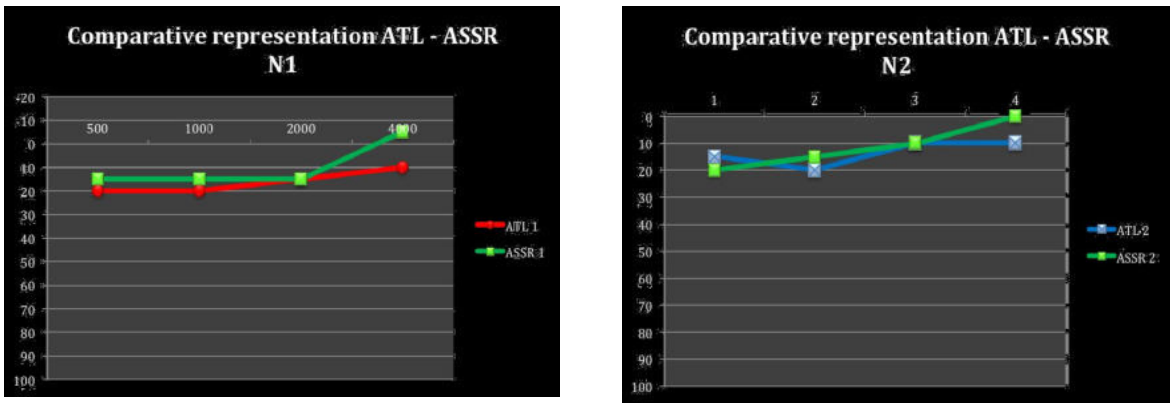
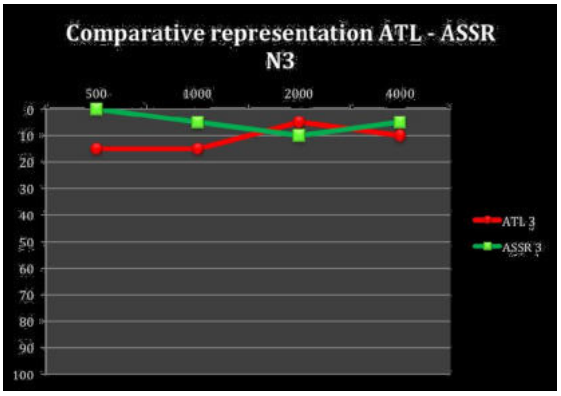


Fig. I.1-2.4. Comparative auditive thresholds ATL/PTA –ASSR for the study units 1 and 2

Comparison of the auditive thresholds for patient I shows a close relationship between the low and average frequencies, the only difference, of 10-15 dB, appearing at 4000 Hz. The audiometric profile is similar left-right, for both ATL and ASSR (fig. I.1-2.4.).

The same profile of the auditive curves, presented comparatively left-right, is also observed for patient II (fig. I.1-2.5), even if 15 dB differences occur bilaterally, on the frequency of 1000 Hz, accompanied by a confluenting tendency of the ATL and ASSR thresholds at 2000 Hz.



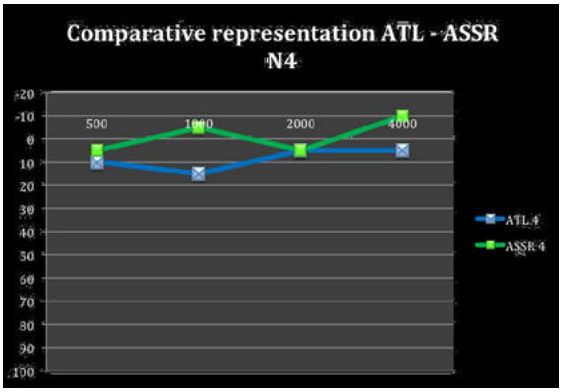
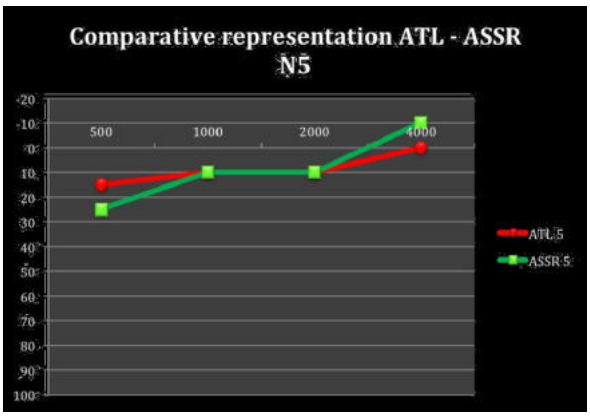


Fig. I.1-2.5. Comparative auditive thresholds ATL/PTA –ASSR for the study units 3 and 4



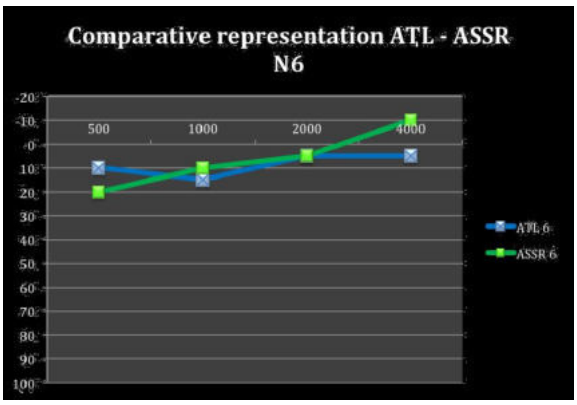
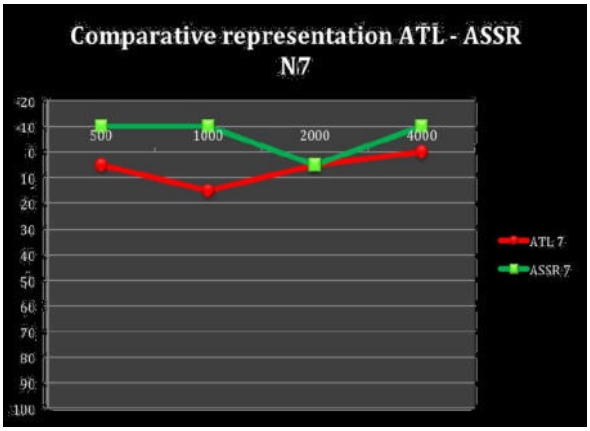


Fig. I.1-2.6. Comparative auditive thresholds ATL/PTA –ASSR for the study units 5 and 6

In the case of patient III, with normal hearing, a good relationship exists between the ATL/PTA and ASSR thresholds, on all frequencies, with a small difference of 10 dB in the extreme points, on 500 and, respectively, 4000 Hz. On both ears, at frequencies of 1000 and 2000 Hz, the ATL/PTA auditive thresholds are similar to the ASSR ones (fig. I.1-2.6).



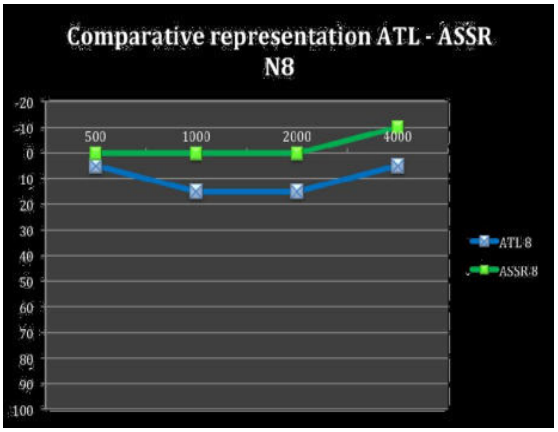


Fig. I.1-2.7. Comparative auditive thresholds ATL/PTA –ASSR for the study units 7 and 8.

For patient IV, the same morphological pattern of curves for both ATL/PTA and ASSR may be observed bilaterally. Differences are noticed for the values of the ATL/PTA-ASSR thresholds of up to 25 dB on 1000 Hz, as well as at lower ones, of 10-15 dB, on 500, 2000 and 4000 Hz, respectively (fig. I.1-2.7).

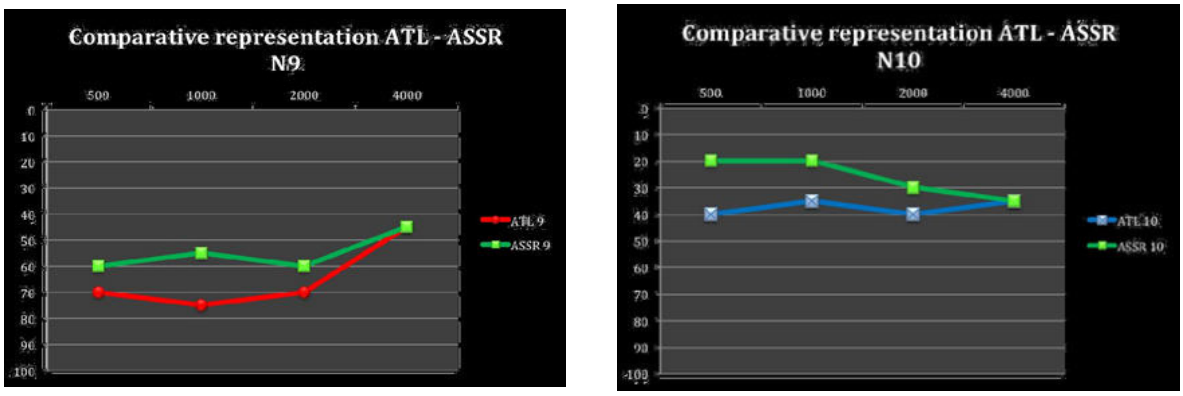


Fig. I.1-2.8. Comparative auditive thresholds ATL/PTA –ASSR for the study units 9 and 10

For the patients with neuro-sensorial hearing loss of different degrees, maintenance of a certain profile of the ATL/PTA – ASSR difference may be observed, described by a difference of up to 15-20 dB on 1000 and 500 Hz, which becomes indistinct at 2000 Hz and disappears at 4000 Hz, where is the same threshold for ATL/PTA, comparatively with ASSR (fig. I.1-2.8).

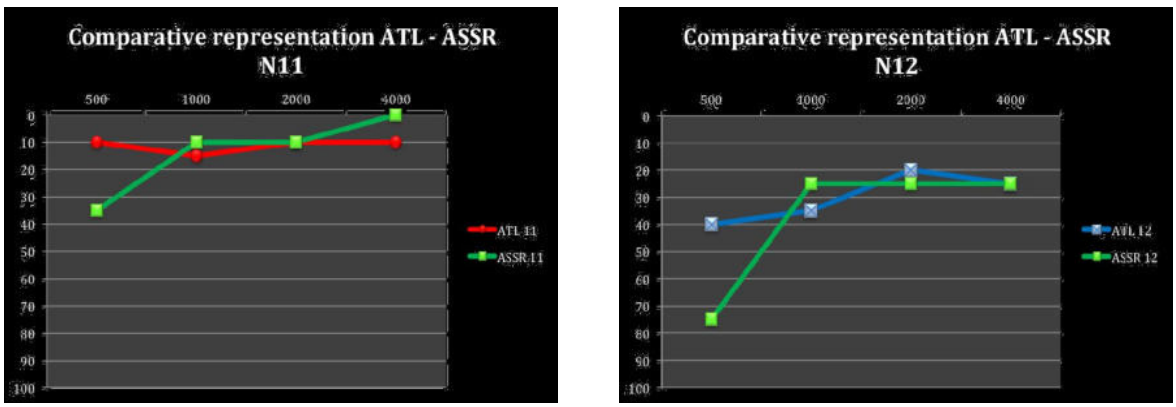


Fig. I.1-2.9. Comparative auditive thresholds ATL/PTA –ASSR for the study units 11 and 12

The case presented in figure I.1-2.9 evidences a significant discrepancy at a frequency of 500 Hz, even if, at the other frequencies, the ATL/PTA values are very close, being even overlapped with the ASSR ones.

Figure I.1-2.10 plots comparatively the ATL/PTA and ASSR thresholds in a patient suffering from otosclerosis. A persistent difference may be observed between the two types of measurements, the values recorded ranging between 15 and 20 dB.

An important observation of the present analysis is that, whichever the main characteristic of the relation between ATL/PTA and ASSR on one ear, the morphology of the ratio of the two curves is the same on the other ear, as well. This might suggest that, apart from the known parameters on which such differences depend, the ones for which the corrections had been already included in the measuring equipment, another factor, related to individual structures, is also involved, which explains why the same type of left-right difference exists between the two types of curves. (Schmulian et al., 2005, Swanepoel, Erasmus, 2007, Swanepoel et al., 2004)

Another objective of the study was to appreciate, for each frequency, the correspondence between the two auditive thresholds.

Figures I.1-2.11 illustrates the ASSR-ATL/PTA relation comparing the values of the auditive thresholds obtained by the two methods.

The weakest relation between the subjective and objective audiometric thresholds (ASSR) occurs at a frequency value of 500 Hz, meaning that the objective threshold is frequently higher than the subjective one, which brings about an objective over-estimation of the real threshold. However, on the other frequencies, the agreement is good, the closest subjective and objective auditive thresholds being obtained on 2000 and 4000 Hz.

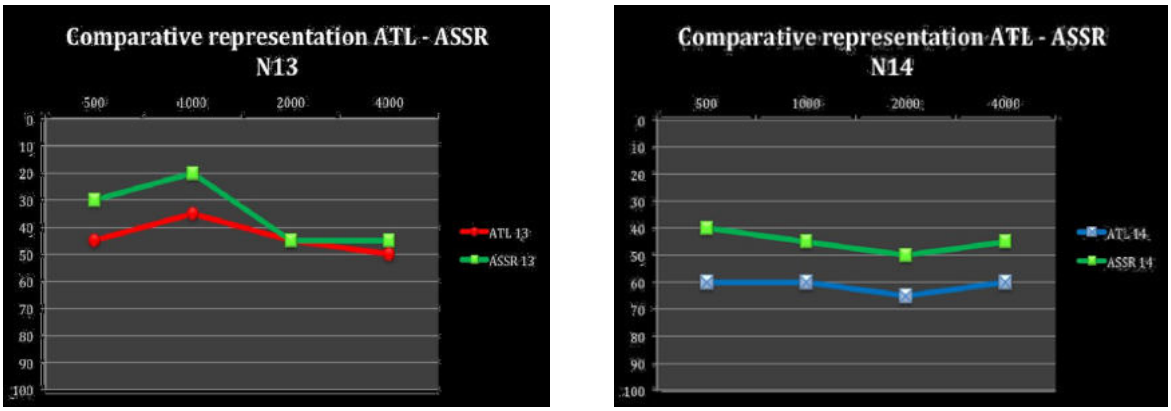


Fig. I.1-2.10. Comparative auditive thresholds ATL/PTA –ASSR for the study units 13 and 14

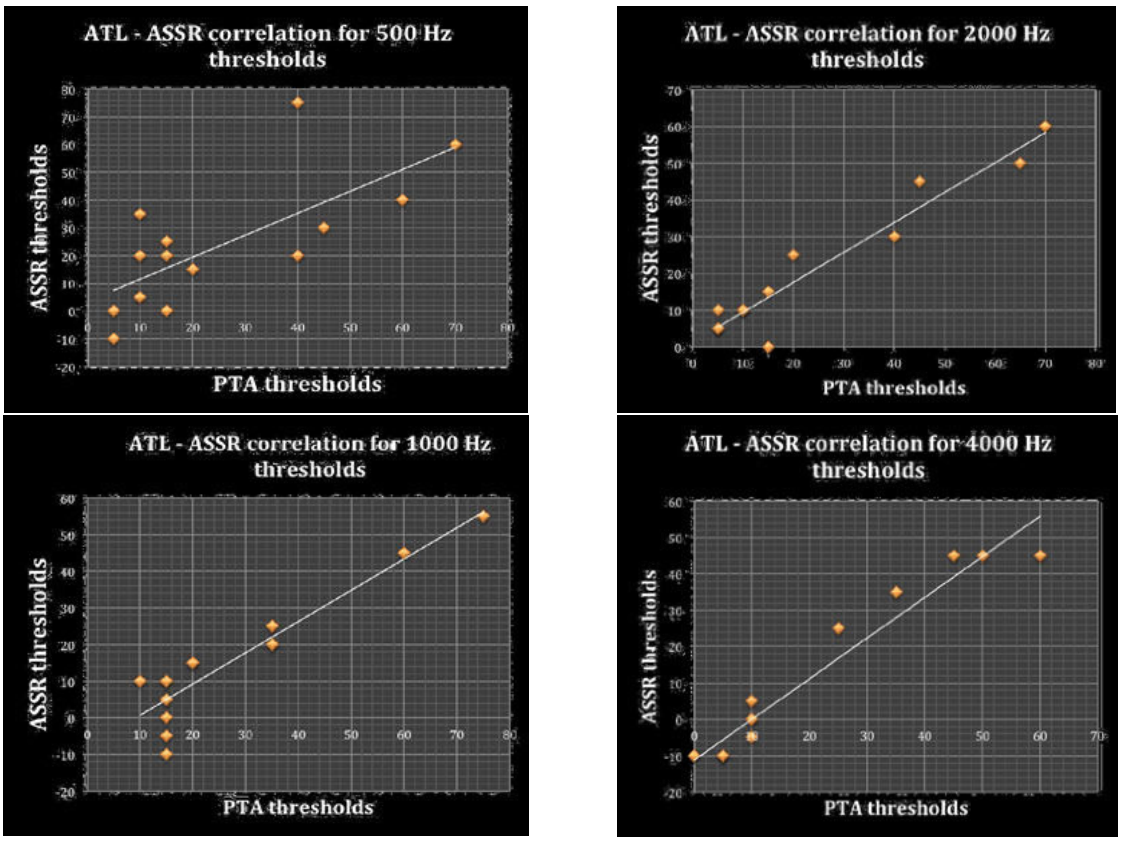


Fig. I.1-2.11. ASSR –ATL/PTA correlation for frequency values of 500, 1000, 2000 and 4000 Hz

The literature of the field describes very few clinical studies devoted to the evaluation of the relation between the subjective and objective tonal audiometric thresholds obtained by ASSR. The results of the present investigation agree with the data published by other authors, since the apparition of ASSR up to now (Ozdek et al., 2010, Ahn et al., 2007, Vander Werff, Brown, 2005).

Conclusions

The differences observed in the present study, between the ATL/PTA and ASSR thresholds are important for 500 Hz, being insignificant for the other frequency values, and permitting, when indicated, a quite reliable auditory rehabilitation by hearing aids, meeting the needs of the child.

An important observation is that, whichever the main characteristic of the ATL/PTA – ASSR relation on one ear, the morphology of the ratio of the two curves is the same on the opposite ear. Such a situation might suggest that, apart from the known parameters on which such differences depend, the ones for which the corrections had been already included in the measuring equipments, there also exists an element related to the individual structures, the presence of which explains why the same type of differences between the two types of audiograms appears on both ears.

To conclude, ASSR represents an objective and reliable method of auditive testing, paying special attention to low frequencies, where some discrepancies may occur.

I.1.2.3. Objective methods for hearing assessement in cochlear implant candidates

Introduction

The cochlear implantation is the procedure by which the patients with profound deafness or with cofosis can benefit of the re-establishment of the auditory function. Cochlear implant indications have changed during the last time by a greater area of indications due to the new knowledge regarding the hypoacusis and to the perfection of the implant itself and of the surgical procedures (Clark, 2003).

Besides subjective tests, the objective tests are important in the cochlear implantation procedure, essential for candidates with the age between 0 and 5 years old and also for the objectivity of the implant indication in borderline situations or special pathologies (Smith et al., 2005, Niparko et al., 2001, Butnaru et al., 2006).

The objective test cad also provides indications for the auditory-verbal and behavioral future of the implanted patient, with the purpose of a proper social insertion (Mârțu et al., 2011).

Brain-stem auditory evoked potentials present a series of clinical applications:

- retrocochlear pathology diagnosis – baeps do not require any supplimentary supraliminary tests or ecochg;
- auditory screening on newborns – it is one of the main screening tests.
- objective estimation of the auditory threshold on difficult patients (small children, psychically challenged persons, stimuli);
- intraoperative monitoring of the auditory nerve; differential diagnosis between transmission and sensorineural hypoacusis (cochlear and retrocochlear).

Although they are capable of hypoacusis detection, they cannot determine the cause of such hypoacusis; this method offers information regarding the existence and the localisation of a lesion in a certain segment of the auditory pathway (Stevens et al., 2013).

BERAs are not capable of offering information regarding the superior auditory structures of the brain stem or the hypoacusis determined by lesions on these levels.

Medium or late latency auditory evoked potentials intervene in such cases.

Medium or late latency auditory evoked potentials are rarely used in the clinical practice, mainly for the assessment of the auditory acuity on low frequencies in children and uncooperant persons. Late latency auditory evoked potentials offer information on the primary and secondary auditory cortex areas, being extremely useful in determining of the tone threshold in non-organic hypoacusis evaluation in adults. They are very sensitive in the vigil/sleep status and in anaesthesia, therefore they are very limited in testing the uncooperative patients (children, psychically impaired persons).

Otoacoustic emissions (OAE) are acoustic signals produced by the cochlea, propagating backwards, through the middle ear, in the external auditory conduct where they can be registered with small microphones (Kemp, 1978, Wilson 1980). The contractile activity of the external ciliated cells represents the mechanical source for the energy of the cochlear amplifier (Prieve, Fitzgerald, 2002). The otoacoustic emissions are a secondary product of the amplified wave; they are retrogradelly transmitted in the cochlea to the stapes and then through the middle ear to the external auditory conduct, where they are registered.

OAE can appear spontaneously or after the auditory stimulation of the ear (evoked oae), implying an intact cochlea and normal outer and middle ear. Spontaneous OAE appear in the absence of acoustic stimulations, in a limited number of normal hearing ears. They do not have a clinical significance. Evoked OAEs are currently used in clinical practice to diagnose the cochlea status.

Main published papers in this field:

- Mârţu Cristian, **Sebastian Cozma**, Luminiţa Rădulescu, Mârţu Dan. Objective Tests for The Evaluation of Cochlear Implant Candidates. *Romanian Journal of Oral Rehabilitation.* 2013; 5(2): 51-53.

Scientific contributions /Clinical implications:

- The study assessed the importance of objective tests in the diagnosis of deafness and the contribution of these tests in formulating the cochlear implant indication. This study was another certainty for the ENT team in the Recovery Clinical Hospital and strengthened the confidence in the audiological assessment for a cochlear implant rehabilitation decision, a method that involves large budgets, surgery in very young children, a special approach from an ethical point of view.

Aim of the study

We proposed an evaluation of the objective tests in establishing a correct indication for cochlear implant in patients with bilateral sensorineural deafness in a group of 34 patients in the ENT Clinic, Clinical Rehabilitation Hospital Iaşi, in the period 2012-2013.

Material and methods

We studied 34 patients with bilateral sensorineural hypoacusis tested by subjective and objective measures with the purpose of an eventual cochlear implantation. We used the following examination procedures:

- subjective methods: pure-tone audiometry (PTA), vocal audiometry (VA), tone and vocal audiometry in free field with and without auditory prosthesis
- objective methods: tympanometry, stapedial reflex (SR), brain-stem auditory evoked potentials (BAEPs), auditory steady state response (ASSR), evoked otoacoustic emissions (OAE).

All the patients included in this study received at least one objective test during the audiometry evaluation in establishing the indication for cochlear implant procedure.

Results

In the study group 34 patients presented bilateral sensorineural hypoacusis tested by subjective and objective methods, 16 females (47%) and 18 males (53%). We assessed 13 children with the age 0-5 years old (38%), 14 with the age between 5 an 18 years old (41%) and 7 adult patients (21%).

The audiometry revealed the following data: 74% of the patients presented a profound bilateral sensorineural hearing loss, 15% a severe type, 4% medium, 3% fluctuant and 4% cofosis (fig. I.1-2.12).

In the age group of 0-5 years old we diagnosticated 10 patients with profound sensorineural hypoacusis, 1 patient with severe bilateral sensorineural hypoacusis and 2 patients with bilateral sensorineural hypoacusis, with a severe form on one ear and profound on the other ear. In the age group of 5-18 years old we diagnosticated 8 patients with profound sensorineural hypoacusis on both ears, 1 patient with moderate form, 1 patient with severe form, 1 patient with bilateral fluctuant form and 3 patients with different degrees of sensorineural hypoacusis on each ear (moderate/profound, severe/profound, severe/cofosis). In the adult patients group (>18 years old), the majority (5 patients) presented bilateral profound sensorineural hypoacusis (71%), 1 patient – the severe form and 1 patient with cofosis.

After the conducted examinations we can observe that patients fulfil the auditory criteria that justify the cochlear implant procedure.

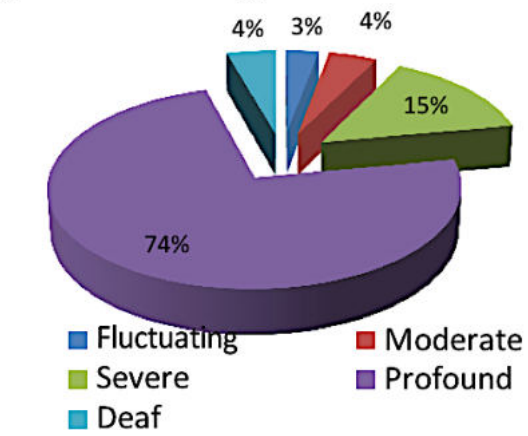


Fig. I.1-2.12. Degree of hearing loss (n= 34)

Discussions

In the age groups after 5 years old (children, teenagers, adults), the implant indication can be supported only by subjective tests; in this category we can include bilateral sensorineural hypoacusis on 3 frequencies on PTA and VA and free field tone audiometry (Deggouj et al., 2007). Twenty-one patients were included in this group. A lack of correlation was observed in the case of patient DO, 63 years old, between the PTA thresholds (severe bilateral sensorineural hypoacusis), free field tone audiometry with auditory prosthesis (medium threshold of 40dB) and free field vocal audiometry with auditory prosthesis which did not offer any answer (0%).

In another case the objective methods were necessary to establish a proper indication for cochlear implant; it was the case of a 6 years old child (CF), with different thresholds on different times in PTA. The ASSR and BAEPs tests offered an objective diagnostic of fluctuant bilateral sensorineural hypoacusis and, according to these tests, we could include the patient in the cochlear implant candidates group.

As a supplementary measure, all the patients evaluated by subjective tests in establishing the possibility for cochlear implantations received at least one objective form of testing. In the case of unrespondent patients to the subjective tests or in case of doubt we use the following objective methods: time, ASSR, BAEP, SR, ECochG, OAE (Ataman, 2002).

In the case of child patients (less than 5 years old) the implant indication assessment is based on objective tests (Sampaio et al., 2011, Deltenre, Van Maldergem, 2013). The electrophysiological methods include tests to obtain an answer to the auditory stimuli independently on the patient's will (Sampaio et al., 2011, Obreja et al., 1998).

The objective methods address to the phsysiological mechanisms of the middle and inner ear (tympanometry, otoacoustic emissions), to neurophysiologic processes of the auditory pathways (electrophysiological methods) or to motor and neurovegetative reflexes provoqued

by auditory stimuli (reflex methods) (Obreja et al., 1998, Cozma, 2008). In this category we can include: standard tympanometry, SR test, measurement of the OAE, of the BAEP and the evaluation of motor and neurovegetative reflexes.

For the patient of 3 years old, we observed the lack of correlation between the thresholds obtained on ASSR (severe bilateral sensorineural hypoacusis on one ear and profound on the other) and the absence of any response on BERA, situation in which the objective tests suggest an auditory neuropathy. In this case of lack of correlation between the two tests, it might be the case of an unfavourable prognosis for the auditory- verbal rehabilitation of the patient because the patients with auditory neuropathy do not obtain the same results on verbal evaluation after the cochlear implantation.

Conclusions

Currently, the objective tests represent an important step in the recommendation for cochlear implant. The obtained data can represent prognosis factors of the evolution after the implant procedure for auditory-verbal rehabilitation on children and for the vocal understanding on adult patients. In all cases (excepting young children) the objective tests are compared/correlated with the subjective tests before the implantation procedure, especially with the subjective evaluation by a conventional prosthesis. The objective tests used can be useful also after the implant procedure in the assessment of the electroneural system.

The comparison between objective and subjective tests (where it is possible) offers information regarding the performance after the cochlear implant procedure (e.g. auditory neuropathy – a poor acquisition of the language).

I.1.3. Research for evaluation of speech understanding and speech production (audio-verbal loop) – original clinical validated tools for Romanian language

Introduction

The development of normal auditory function is a dynamic process that involves permanent changes in the structures of the peripheral and central auditory nervous system and is essential in the first years of life as a premise of language formation and communication for social, emotional and cognitive development of the child. These changes occur naturally in response to stimulation, and even a mild or partial hearing loss can affect a child's ability to develop properly, especially if it occurs during the critical period (Litovsky, 2015). Important physiological processes of development and maturation of the auditory system take place before birth and especially in the first few months after birth, being largely complete towards the end of the first year of life. In people with normal hearing, the optimal functionality of the auditory pathway is already reached towards the end of the second year of life (Tallal, Gaab, 2006). Communication and speech pathology in children is determined mostly by hearing loss and less frequently by neurological or psychological disorders.

Auditory Neuropathy Spectrum Disorder (ANSD) also known as Auditory Dyssynchrony (AD) or Auditory Neuropathy (AN) is a special category of auditory disease. The dysfunction of auditory system could be explain by three topographic lesions: the damage of internal hair cells of organ of Corti, the synaptopathy (dysfunction in neurotransmission in synaptic space from internal hair cells of cochlea to the first neuron of auditory pathway from Corti ganglia) and the third is the auditory nerve dysfunction - electrical signals received from the cochlea and transmitted to the brain are dyssynchronous. In any of these conditions the auditory signals are not synchronized so information is not relayed to the brain in a clear and consistent manner. The clinical manifestations of auditory neuropathy/dyssynchrony vary from near normal hearing to profound hearing loss in pure tone audiometry but with bad or no speech recognition (Kaga, 2016, Norrix, Velenovsky, 2014, Starr et al., 1996, Kaga et al., 1996).

Auditory Processing Disorder (APD) also referred to as Central Auditory Processing Disorders (CAPD) is characterized by difficulty hearing and understanding speech even though no measureable hearing loss exists. Children with APD may exhibit a variety of listening and related complaints such as difficulties in understanding speech in noisy environments, following directions, and discriminating similar-sounding speech sounds (Heine, O'Halloran, 2015, Bellis, Bellis, 2015).

Testing language comprehension in the early years of life and making an early and complete diagnosis of hearing impairment that allows for optimal rehabilitation within the right time frame to achieve the best results is especially important (Tallal, Gaab, 2006, Bourgeois et al., 2000). If a hearing aid is not provided by a critical time, it may act on an already degenerate, inefficient hearing system and preprogrammed neural structures may lose their function permanently or it would not be able to develop enough (Ruben, 1997).

Main published papers in this field:

- Raluca Olariu, Oana Bitere, D. Mârțu, C. Mârțu, Luminița Rădulescu, **S. Cozma**. Strategies for testing language comprehension in young children. *The Medical-Surgical Journal.* 2018; 2(s. 1): 151-163. ISSN: 0048 - 7848
- **Sebastian Cozma**, Cristina Gena Dascălu, Luminița Rădulescu, Cristian Mârțu, Oana Bitere, Dan Mârțu, Raluca Olariu. Audiological Clinical Validation of New Original Romanian Speech Audiometry Materials for Evaluation of Communication Abilities in Children of Primary School Age. *Review of Research and Social Intervention.* 2016; 55: 47-62. (IF=0,380)
- Raluca Olariu, Luminița Rădulescu, Oana Bitere, Cristian Mârțu, Cristina Hera, Vasilica Toma, Dan Mârțu, **Sebastian Cozma**. Clinical validation of new original romanian speech audiometry materials for teenagers and adults. *ORL.ro.* 2018; 39(2): 24-30. ISSN 2067-6530
- Cristina Gena Dascălu, **Sebastian Cozma**, Gabriel Dimitriu, Mihaela Moscalu, Raluca Olariu. A mathematical method to validate new Romanian speech audiometry materials for evaluation the hearing level in young and adults. *Proceedings of The 13th International Scientific Conference eLearning and Software for Education*, Bucharest, 2017: 522-528. DOI: 10.12753/2066-026X-17-252.

Scientific contributions /Clinical implications:

- This complex research, which lasted several years, led to the development of the first set of tools for testing the speech comprehension in Romanian calibrated and clinically validated.
- The test battery was created and validated for all age categories: toddler, preschool, school, teenager and adult, covering all levels of language development.
- This set of tests developed by our research team is being registered at OSIM (State Office for Inventions and Trademarks) and will be made available to colleagues across the country as a working tool in assessing voice discrimination, diagnosing hearing loss and assessing hearing rehabilitation in children and adults.
- The creation of the testing tools was computer-assisted, using for the first time in the world a software specially designed for this purpose and a unique methodology, which is not found in any specialized publication so far.
- The originality of the research is also underlined by the use in the clinical validation and processing of statistical data of an algorithm specially designed in order to compare the test results with the theoretical ideal.

The first standardized lists of syllables used in audiometry tests were developed by Campbell and Crandall in 1910, at the Bell Laboratories. Each list contained 50 items, among which 5 items were consonant – vowel, 5 were vowel – consonant and the other 40 items were consonant – vowel – consonant. Since then the researches in this area grown up and the test materials were continuously improved, as well as the technology used for testing. It is mandatory to develop customized tests practically in each country, as the scientific literature already showed. For example, in the USA the most common tests used in speech evaluation is Harvard Phonetically Balanced (PB-50) Word Lists, Central Institute for the Deaf (W-22) Monosyllabic Word Lists and the Maryland CNC Test developed by Causey et al. (Causey et al., 1984). In United Kingdom the materials used are the Fry tests for speech audiometry (Fry, 1961), the Manchester Junior word list (MJ) for children and the Arthur Boothroyd (AB) list for adults and teenagers (Westhorp, 2020). In France the most known are the phonetic tests of JC Lafon for children (Lafon, 1956) and the monosyllabic and bisyllabic words list of Fournier (Fournier, 1951), and in Germany it is used the so-called Freiburg speech intelligibility test, developed by Karl Heinz HahIbrock (Feldmann, 2004).

For the Romanian language such an audiological test battery has not been created so far, and it is not possible to translate or to adapt other languages speech tests, because of the phonetic and morphological characteristic features (Johns et al., 2012); the tests must contain the most commonly used words, phonetically balanced, and the rules from one language are not applicable for the others, because the syntax and the semantics are totally different.

Original method for the creation of the Romanian linguistic material for speech discrimination battery test. As part of a doctoral research project deployed in Audiology-Vestibulogy Department of Rehabilitation Clinical Hospital, Iaşi we have developed and clinically validated the first original and complex speech audiometry material in Romanian, adapted to all age groups, including also with preschool age group, the very young children category (under 3 years) the young people and adults age category and primary school age category (Cozma et al., 2016).

Our results for a work that has been made along over 3 years were published in few articles in international database indexed journals as ISI WoS or Index Copernicus.

I.1.3.1. Speech discrimination in small children – strategies for a challenging task

Background

Erber describes a matrix of auditory abilities useful in understanding speech perception tests by tracking four main tasks in assessing auditory performance: detection (the ability to signal when a sound stimulus is presented), discrimination (the ability to determine whether two stimuli are identical or different), identification (the ability to recognize the presented stimulus and to identify by repeating, pointing or writing and is assessed by word recognition tests) and comprehension (the ability to understand the meaning of the stimulus; the child can indicate a picture and may indicate that he understood the stimulus or may just repeat the word without understanding it, a process that represents identification) (Erber, 1980).

The general assessment scales of the components of perception-comprehension and expression of language Categories of Auditory Performance Scale (CAP) and respectively the Speech Intelligibility Rating Scale (SIR) are tests with a wide use, relatively easy to use both by specialized staff and by family, relatives, but has the disadvantage of a general description of auditory performance with difficulty in fitting and classification of particularities (Archbold et al., 1995, Cox, McDaniel, 1989). Behavioral audiometry can be applied depending on the child's age and skills: Observational Behavioral Audiometry (BOA), Visual Reinforcement Audiometry (VRA) but Conditioned Play Audiometry (CPA) but offering inaccurate

information in case of assessment of the child's hearing (Karikoski, 1998). The development of strategies for assessing language comprehension in the age category 0-3 years, a group in which the level of language development is variable and the ability to focus on these tests is different for each child and generally reduced, should focus on the particularities of age development.

Materials and methods

The linguistic database corresponding to the age group under 3 years was created by consulting the *Curriculum for the early education of children aged between 3 and 3 years* and the *Curriculum for the early education of children aged between birth and 6/7 years* - documents prepared by the Ministry of National Education and Scientific Research that regulate the education of preschool and preschool children, but also the fund of books for children available in Romanian for this age. The available words are few, being selected only those that represent concrete notions (communication at this age is focused on what is perceptible in concrete terms), easily recognizable by the child. The choice of words was aimed to cover the representation of all the phonemes of the Romanian language represented in the " speech banana". I used the articulated forms of the words that I introduced in commands and simple questions such as "Show!", "Which is it? ",“ Where is it? ” to train the child "through play" and allow us to affirm the identification and understanding of the word; this will allow us to quantitatively assess speech intelligibility in the tests we have developed. In the context of the age peculiarities presented above, it was necessary to use the image representation of words and thus icons were created with appropriate dimensions and characteristics to be easy to use and spot. The speech comprehension testing methodology was based on the playing game, held in the test room, ensuring a familiar environment, comfortable by the presence of the parent, the close person and the team of examiners.. The running of the lists of sentences was done in the open field, due to the difficulty of accepting the supraaural headphones at this age. At this age group it is difficult to fully test all intensities in the same child so we chose testing at 30 dB SPL, 40 dB SPL, 50 dB SPL and 60 dB SPL, these intensities providing an ideal hearing input specific to whispered voice and spoken voice. The child's recognition of the corresponding picture validated the command from the tested list.

Results. The results obtained by running the lists of sentences (simple commands / questions) for the 10 children under 3 years of age are shown in figure I.1-3.1. The speech recognition scores for the tested intensities exceeding 90%, with values of 100% for the test intensities of 50 dB SPL and 60 dB SPL. We consider that the development of this test with limited words, in limited time is adapted to our need to define the ability of that child to develop his language based on speech comprehension.

Discussions

The role of language comprehension testing in hearing-impaired children rehabilitation. In cases of sensorineural hearing loss with rehabilitation by conventional prosthesis or cochlear implant, language comprehension testing allows the assessment of the evolution of auditory performance in these children, essential especially after reaching normal tonal thresholds with the hearing aid. Follow-up the evolution of speech recognition scores allows quantifying the benefits of hearing rehabilitation, tracking the evolution of hearing performance over time, identifying problems after hearing rehabilitation (hearing impairment or damage to devices), identifying specific speech detection errors that need remediation, demonstration of speech rehabilitation needs, help in selecting the most suitable educational environment. Degradation of speech comprehension in young children when liminal tonal thresholds with conventional hearing aid are not correlated with speech recognition scores, may indicate poor speech comprehension and the need for cochlear implantation (van Wieringen, Wouters, 2015).

The role of language comprehension testing in auditory neuropathy spectrum disorders. Their therapeutic management is a real challenge for all professionals involved in

the field of education and clinical audiology. The benefits of cochlear implantation as early as possible in children with auditory neuropathy are represented by the possibility of normal development of auditory function with the acquisition and proper development of language closely related to the child's age at diagnosis and at the time of implantation, the process of speech therapy (Gökdoğan et al., 2016). Studies have shown similar post-rehabilitation outcomes in children with neurosensory hearing loss and those with auditory neuropathy who have had a cochlear implant (Fernandes et al., 2015).

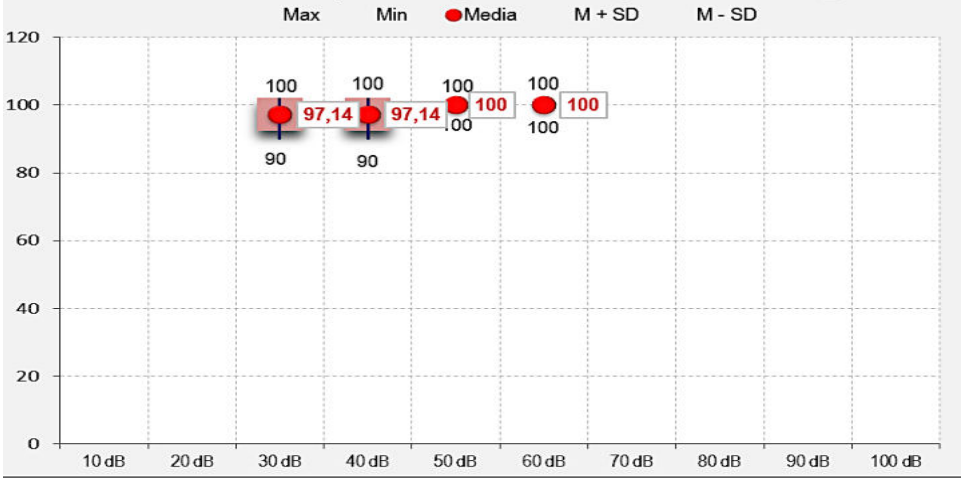


Figure I.1-3.1. Word Recognition Score (WRS) % for all tested intensities in 0_3.S group

The role of language comprehension testing in deafblindness / multiple sensory deficiencies. Assessment of hearing and language comprehension in these cases, whether congenital or acquired, is important because there is a wide variation in hearing disorders in the condition and depending on the degree of hearing loss or other impairments, forms of communication may vary or coexist. The assessment is individualized in these cases and must establish an auditory diagnosis in the context of a complex multidisciplinary assessment. Cochlear implantation is not contraindicated in children with prelingual congenital deafness with additional disabilities, but studies have shown limited progress in language and communication development in subjects with deafblindness and in children who have been further diagnosed with autism compared to those with other disabilities. (attention deficit, learning disorders, hyperactivity syndrome, mild or moderate mental retardation, cerebral palsy) and who have benefited from a cochlear implant (Daneshi, Hassanzadeh, 2007). Testing language comprehension in children with deafblindness pre- and post-hearing rehabilitation allows the establishment of a complex plan for recovery and integration of these children, following the use of residual or recovered hearing in the individualized intervention program (Byun et al., 2013).

Conclusions

Testing language comprehension in young children is essential especially if around the age of 1.5 - 2 years there are no first manifestations of expressive language. The plasticity of the child's auditory system is maximum in the first period of life, when the brain stores an enormous amount of information, and the period of up to 2-3 years is crucial in learning the language, a 3-year-old child can already fluently hold a conversation.

Our research has led to speech recognition tests creation, tests that have been applied using various indications or prompts as pictograms adapted to this age range, being then clinically validated by statistical studies. Thus, specific efficient tests in Romanian are made available to specialists in the field of audiology and speech therapy.

I.1.3.2. Speech discrimination in preschool and school children, teenagers and adults – an indispensable tool for audiological evaluation

Background

Speech audiometry has become a fundamental tool in audiological assessment whereas in conjunction with pure-tone audiometry, it can aid in determining the degree and type of hearing loss. Speech audiometry also provides information regarding speech understanding and word recognition abilities (ASHA, 2015, ASHA, 1988). In addition, information gained by speech audiometry can help assessing the effectiveness of hearing rehabilitation by conventional or implantable prosthesis, also facilitating audiological rehabilitation management. Understanding speech involves the perception of pure tones but also complex cortical processes, being necessary to use speech as a stimulus to create a testing situation as close as possible to the real communication environment of the person being tested (ASHA, 2015, Johns et al., 2012). The assessment of speech discrimination has to include speech audiometry material according to age and psychoneural condition and any clinical test material should contain equivalent and phonetically balanced lists, linguistically adapted to all age categories (Johns et al., 2012, Krull et al., 2010, Mendell, 2008).

Aims of the researches

Our purpose was to demonstrate that any generated list with our algorithm can be clinically used with a high degree of confidence. Thus, the same results should be obtained across multiple measurements with randomized different lists presentations in similar standard testing conditions without statistically significant differences between all presented word lists.

Another main objective of our study was to demonstrate for the normal hearing children that the words recognition in quiet across our lists is statistically related to the linguistic normality for this interval of age – to obtain the clinical validation for the battery test for all age groups.

Materials and methods – common for all groups

The including criteria except the specific age for each group, were: normal aspect of the ear, bilateral normal hearing and age-appropriate cognitive and linguistic development, good pronunciation, Romanian native speakers. All patients have been auditory assessed in Audiology Department of Rehabilitation Clinical Hospital Iași, Romania, with their informed consent of with the parents informed consent for children. For all the subjects of the group have been conducted otomicroscopy, tympanometry and pure tone audiometry. We included in the study patients with normal aspect of the ear, tympanometry of type A (normal) and a pure tone threshold ranging from 0 to 20 dB for every tested frequencies in pure tone audiometry (250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz). For small children that not collaborate to the pure tone audiometry we used the otoacustic emissions (distorssion products) in order to sustain the normal hearing. All audiometric assessment took place in a double-walled, sound-treated room in Audiology Department. The Interacoustics audiometer AD629 was calibrated according to actual audiometry standards. The pure tone audiometry (PTA) and also the speech audiometry were made using closed circumaural headphones (Sennheiser HDA 200). The Hughson-Westlake method was used for PTA procedure and the results were stored for further analyses in the database. Speech perception was tested monaurally in quiet using the new speech audiometry material.

The phonetically balanced word lists were generated using our own and original algorithm. A balanced list should expose the tested subject to all frequencies spectrum of common spoken language approximately in the same manner that it is naturally exposed to a long speech. The algorithm extracted by spectral-statistics analysis of a Romanian spoken language corpus, the ideal criteria used in list generation. In this way, the frequency spectral

characteristic for every list is very similar to ideal distribution of whole speech and the generation of lists was based on genetic algorithms.

The test material was created in different but interdependent stages, based on research and scientific support. In a first stage, the linguistic database for adults and older children was developed using as main sources the *Explanatory Dictionary of the Romanian Language* (DEX), 2nd Edition and the *Orthographic, Orthoepic and Morphological Dictionary of the Romanian Language,* 2nd Edition (Academia Română, 2010, Academia Română, 2012). An original computer module was created to determine the frequency of use of words in spoken Romanian. This computerized selection tool, based on a computer calculation algorithm, selected the most frequent words in Romanian by browsing 765,000 media pages totaling over 350 million words. The selected words were recorded audio professionally in the recording booth belonging to the Iași Regional Studio of the Romanian Television, using a female voice, a native romanian speaker. The recorded audio material was edited and lists of 10 test units were generated. The lists were phonetically balanced using a computer algorithm for frequency spectral analysis, each finally respecting the frequency spectrum of the spoken Romanian language. For every subject included in our study (except the very small children) the pure tone average was determined in every ear using 3 frequencies (3 FAHL – Three Frequency Average Hearing Level: 500 Hz, 1000Hz and 2000 Hz) and also 4 frequencies (4 FAHL – Four Frequency Average Hearing Level: 500 Hz, 1000Hz, 2000 Hz and 4000 Hz). The lists were presented at different intensities to all patients so each list to run at all intensities. For every list at a certain intensity was determined the Word Recognition Score (WRS - the percent of correctly recognized words) and for every tested ear were calculated the SRT (Speech Recognition Threshold meaning the minimum hearing level for speech at which an individual can recognize 50% of the speech material) and the Maximum Recognition Threshold (MRT - minimum hearing level for speech at which the highest percentage of words are recognized). The coding used for the generated lists was 1_3, 3_5, 5_7 or 7_12 – for the age range followed by word syllable category: B for bisyllabic words lists, M for monosyllabic words lists and L for logatoms and the list number with Arabic letters (e.g. 7_12.B.1 for the first list of bisyllabic words). Statistical analysis of data was performed using software package SPSS 20.0.

Particularities of the research for each age group:

1. Research for children of preschool age

The study group included a number of 51 preschool children aged between 3 and 7 years divided in 3-5 years subgroup (19 subjects) and 5-7 years subgroup (32 subjects).

Particularities: The audiological testing protocol included tympanogram, Distortion Product Otoacoustic Emissions testing (DPOAE) measured for 0,5 to 10 kHz frequencies and the speech audiometry using the new original material. The age was not appropriate for using the pure tone audiometry.

New original tool to be clinically validated: The phonetically balanced words were grouped in 20 bisyllabic words lists and 10 monosyllabic words lists, generated using our own original algorithm. Speech perception was tested monaurally in quiet.

2. Research for children of primary school age

The study group included a number of 24 children (equivalent to 48 ears or test units) aged between 7 and 12 years.

Particularities: The linguistic material for speech audiometry has been gathered based on the principles of early preschool education curriculum and primary school program developed and approved by Ministry of Education and Scientific Research from Romania. We created a language corpus for primary school aged children using the most frequently words according to school textbooks available for this stage.

New original tool to be clinically validated: We generated with our original algorithm 50 bisyllabic words lists and 20 monosyllabic words lists, every list containing a number of 10 words, corresponding to the most actual languages speech audiometry tests.

3. Research for teenagers and adults

The study group included a number of 51 subjects with the age over 12 years old (mean age of 33,9 yo).

Particularities: For this group of age, every person could recognize and discriminate any word from the spoken language, so our source for the corpus was the written materials from the internet, on very common topics. We used the above described digital algorithm.

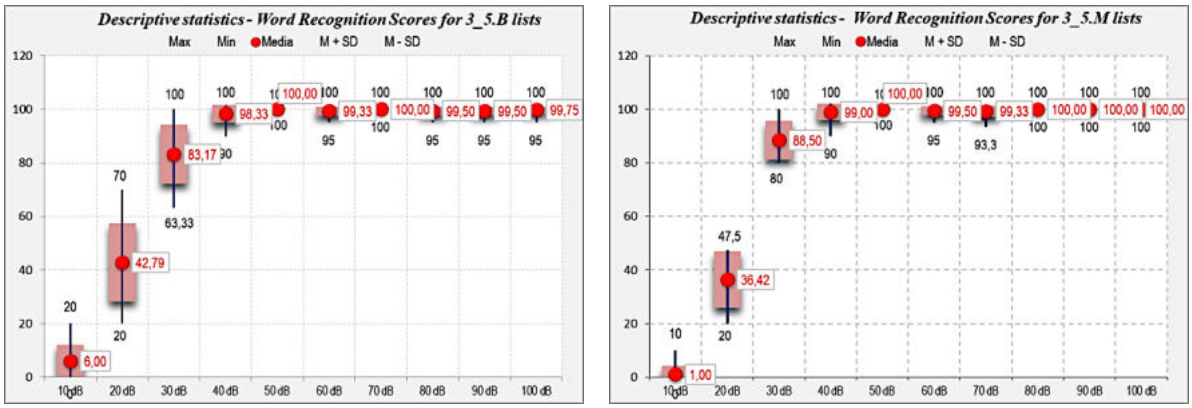
New original tool to be clinically validated: Using our original algorithm we created 80 bisyllabic words lists , 30 monosyllabic words lists and 20 lists with logatomic units, every list containing a number of 10 words or units.

Results and discussions for study groups

1. <u>Research for children of preschool age</u>

Results

Descriptive analysis of the data indicated a relative homogenous subgroup of study for 3-5 years of age with 47,4% of girls and 52,6% of boys and more heterogenous for 5-7 years subgroup with 37,5% girls and 62,5% boys. The majority of subjects of 3-5 years subgroup were tested with bisyllabic words lists only – 47,4% and both bisyllabic and monosyllabic words lists – 47,4%, increasing the reliability of both categories of tested words, while in 5-7 years subgroup 71,9% of children were tested for both bisyllabic and monosyllabic words lists and only 25% for bisyllabic words lists and 3,1% for monosyllabic words lists showing increased testing compliance with older age.



a. **b.**

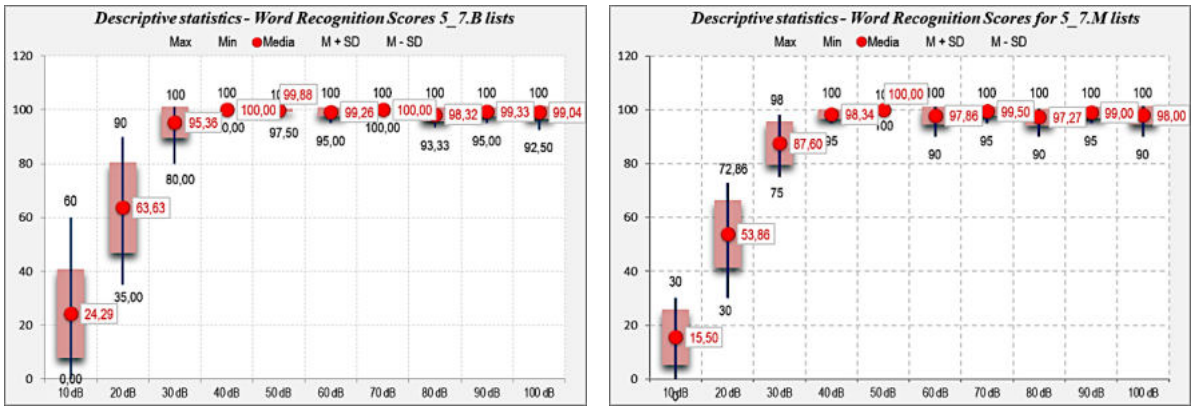
Figure I.1-3.2. Descriptive statistics – percentage of recognized words in 3-5 years subgroup for a. bisyllabic lists – **3_5. B**; b. monosyllabic lists – **3_5. M**.

Note: Abscissa – intensities – dB SPL; Ordinate – Word Recognition Score (WRS) %

The statistical analysis of the main audiological parameters for the two types of words lists aimed to compare the mean SRT and MRT for each subgroup, considering all tested ears equivalents as test units. For the bisyllabic tested lists we found a mean of SRT of 22,42 dB SPL corresponding to -2,42 dB HL and a mean MRT of 39,39 dB SPL corresponding to 19,39 dB HL in the 3-5 years subgroup. For the monosyllabic tested lists, we registered a mean SRT of 21,84 dB SPL corresponding to 1,84 dB HL and a mean MRT of 39,47 dB SPL corresponding to 19,47 dB HL in the 3-5 years subgroup.

In the 5-7 years subgroup we registered for the bisyllabic tested lists a mean SRT of 17,02 dB SPL corresponding to -2,82 dB HL and a mean MRT of 32,10 dB SPL corresponding to 12,10 dB HL. For the monosyllabic tested lists, we registered a mean SRT of 18,44 dB SPL

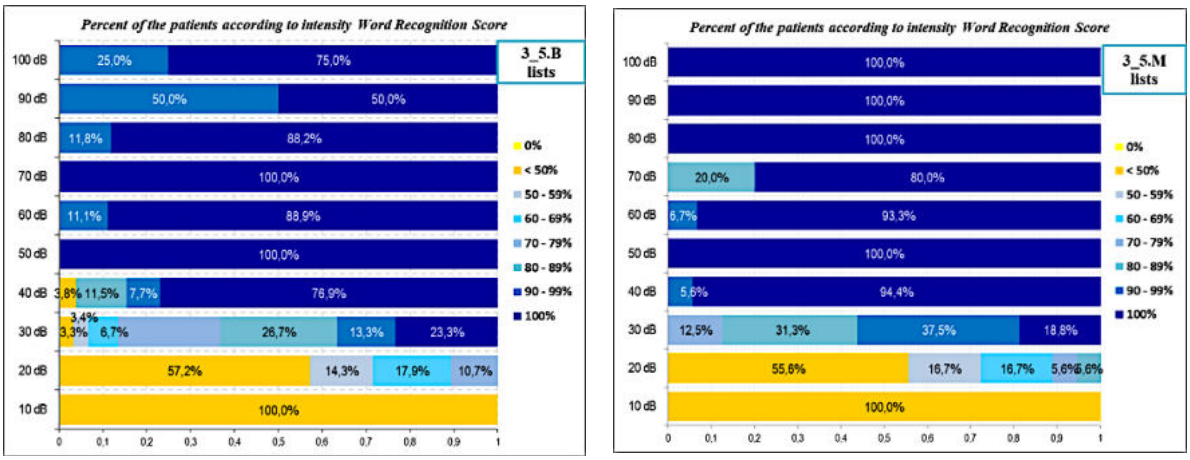
corresponding to -1,56 dB HL and a mean MRT of 37,71 dB SPL corresponding to 17,71 dB HL.



a. **b.**

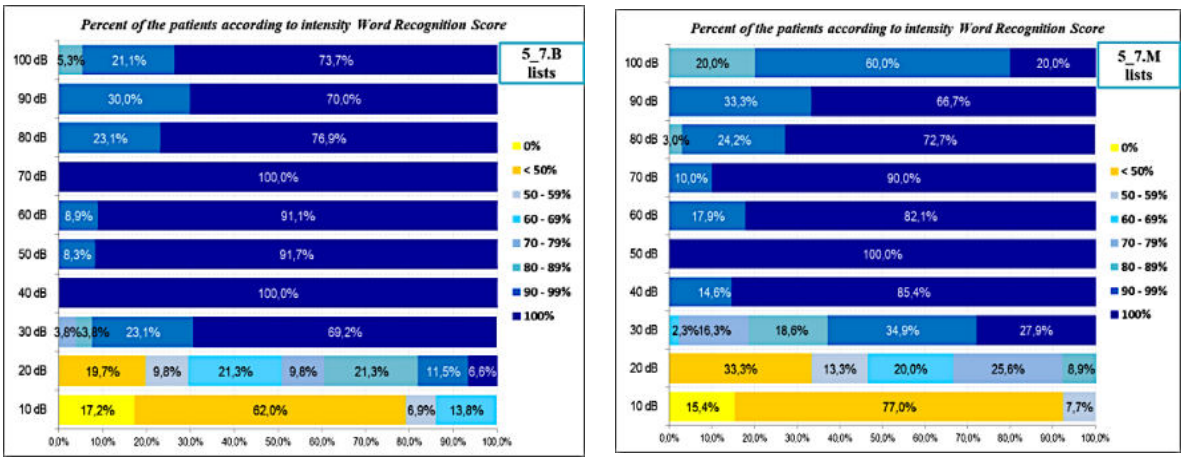
Fig. I.1-3.3. Descriptive statistics – percentage of recognized words in 5-7 years subgroup for a. bisyllabic lists – **5_7. B**; b. monosyllabic lists – **5_7. M.**

Note: Abscissa – intensities – dB SPL; Ordinate – Word Recognition Score (WRS) %



a. **b.**

Fig. I.1-3.4. Percent of the patients according to Word Recognition Score for all intensities in a. bisyllabic words lists – **3_5. B**; b. monosyllabic words lists – **3_5.M**.



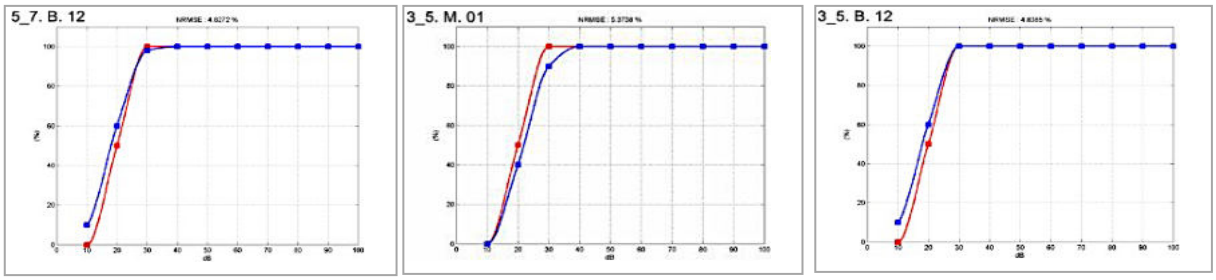
a. **b.**

Fig. I.1-3.5. Percent of the patients according to Word Recognition Score for all intensities in a. bisyllabic words lists – **5_7. B**; b. monosyllabic words lists – **5_7. M**

One of the most important and relevant audiological parameters is Word Recognition Score (WRS) for the 10 words lists for every tested intensity from 10 dB SPL to 100 dB SPL, with great importance for the 10 to 40 dB SPL in defining the shape of vocal audiogram. For every intensity there are represented the mean of WRS with standard deviation intervals and the maximum variation. The figures I.1-3.2 and I.1-3.3. highlight this parameter for bisyllabic and monosyllabic lists in the two subgroups of age. It is easy to observe that the mean WRS riches over 95% at 30 dB SPL for both types of lists, starting with 40 dB SPL is constantly over 99% for all bigger intensities for bisyllabic lists and over 98% for monosyllabic lists. This observation suggests that the speech recognition is a little more difficult for monosyllabic words, in agreement with all well-known principles of speech recognition tests.

It was realized the percent distribution of all subjects according to Word Recognition Scores categories for the two groups of tested lists. In 3-5 years, subgroup, for bisyllabic and monosyllabic lists presented at 40 dB SPL over 75% of children understood 100% of words and at 50 dB SPL over 97% present 100% intelligibility (fig. I.1-3.4.a and I.1-3.4.b). As the level of presentation increases, we can note a tendency for decrease of intelligibility (less than 100%), but still rest for all subjects between 90 and 99%. Scores below 89% are shown only at intensity levels less than 40 dB SPL. In the 5-7 years subgroup almost 70% of the subject recognized 100% of the bisyllabic words at 30 dB SPL intensity and over 90% to 100% WRS over 40 dB SPL – fig. I.1-3.5.a. For the monosyllabic lists fig. I.1-3.5.b in 5-7 years subgroup the intensity level of presentation had to exceed 40 dB SPL to achieve the majority of subjects with 100% intelligibility (over 85%) and the rest between 90 and 99% (14,6%).

We note two differences between monosyllabic and bisyllabic lists: the maximum of speech performance is present at 30 dB SPL for bisyllabic lists and at 40 dB SPL for monosyllabic lists and the intelligibility decreases slightly more for monosyllabic lists at 100 dB SPL intensity. We determined for every tested list the Normalized Root Mean Square Error (NRMSE) parameter, demonstrating the correlation of the curve we obtained with an ideal speech comprehension curve. In fig. I.1-3.6 we had some examples of graphical representation and values for NRMSE parameter in randomly selected lists.



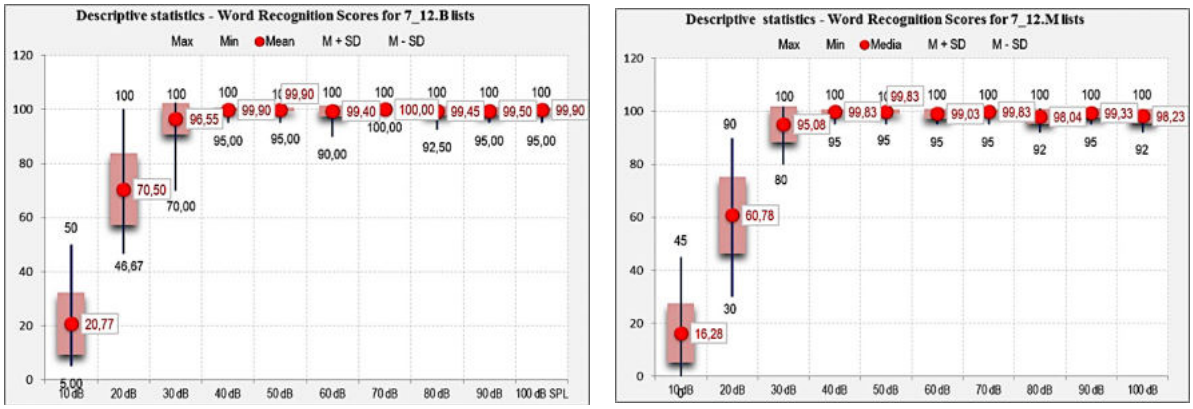
a. **b.** **c.**

Fig. I.1-3.6. Graphical representation and values for NRMSE parameter in randomly selected lists: a. **3_5B. 12** list; b. **3_5M. 01** list; c. **5_7B. 12** list

Discussions

The speech perception and speech recognition are providing important information regarding overall auditory perception skills and can be extremely valuable in prognosis of the speech, language, reading and cognitive abilities of preschool children. Speech perception assessments must provide accurate measurements of a child's ability to perceive phonetic segments and patterns, words, sentences and connected discourse, because decisions about amplification with hearing aids, cochlear implantation and can provide important information regarding the planning and implementation of additional forms of audiologic (re)habilitation (e.g., speechreading, auditory training, perceptual training, etc.) being useful in monitoring a child's progress (Mendell, 2008). Speech audiometry in young children can be a useful tool

providing arguments for cochlear explantation in special cases (significant pre-operative ossification and with no benefit in speech perception and speech production) but should be not the decisive as long as tonal stimuli are still perceived, with an important role in receiving the acoustic alarm signals (Radulescu et al., 2013). Speech perception skills must be assessed routinely using valid and reliable clinical assessment methods suitable for infants and young children (Mendell, 2008, Cozma et al., 2016, Yoshinaga-Itano, 2014). The appropriate tests of speech perception performance in children should respect several criteria: the cognitive, motoric, and attentional demands of the test should be age-appropriate, performance should be independent of higher-level language abilities being appropriate to a linguistically common level, tests should ultimately assess a person's ability to communicate in everyday situations (Mendell, 2008, Yoshinaga-Itano, 2014, Uhler et al., 2017). Creating a language corpus for preschool aged children based on early preschool education curriculum approved by Ministry of Education and Scientific Research from Romania, we reached the goal of word familiarity and age-appropriate linguistic level. We also created phonetically balanced words lists using an original generation algorithm. The absence of failure in speech recognition among the subjects as well as the absence of 100% for all children at more than 40 dB of presentation sustains the high quality of elaborated material. In our study, the results for the entire study group in monosyllabic words and bisyllabic words tested lists showed parameters that fit with the normal vocal audiogram slope. The variability of the responses for normal hearing children in this group of age allows us to describe not just a regression line, but an area of the speech intelligibility audiogram that defines the normality (fig. I.1-3.7. a and I.1-3.7.b).



a. Bisyllabic lists *b. Monosyllabic lists*

Figure I.1-3.7. Descriptive statistics – percentage of recognized words.
Abscissa – intensities - dB SPL; Ordinate – Word Recognition Score (WRS) %

2. ***Research for children of primary school age***

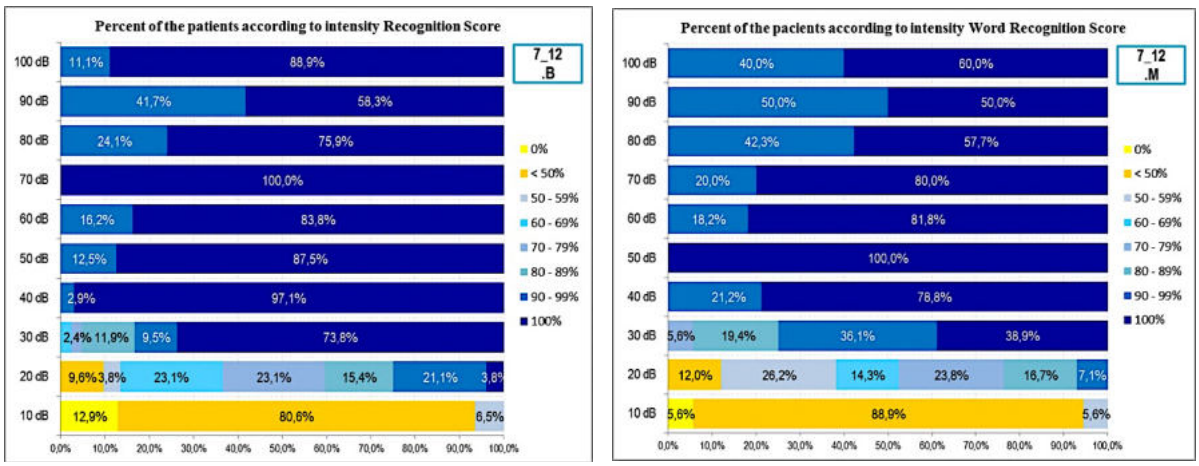
Results

We present the clinical validation of a new and original audiological speech understanding test useful in evaluation of communication abilities in primary school children.

Descriptive analysis of the data indicated a relative homogenous group of study with 40 % of boys and 60 % of girls tested and having a balanced age distribution between 7 and 12 years with a mean of 9 years (SD = 1.384). The majority of subjects of our group (80%) were tested with both bisyllabic and monosyllabic words lists, increasing the reliability of both categories of tested words, while 16% have been tested only with bisyllabic lists and 4% only with monosyllabic lists. One of the most important and relevant audiological parameter is Word Recognition Score (WRS) for the 10 words lists for every tested intensity from 10 dB SPL to 100 dB SPL, with great importance for the 10 to 40 dB SPL in defining the shape of vocal audiogram. For every intensity there are represented the mean of WRS with standard deviation

intervals and the maximum variation. The figures I.1-3.7. *a* and *b* highlights this parameter for bisyllabic and monosyllabic lists. It is easy to observe that the mean WRS riches over 95% at 30 dB SPL for both types of lists, starting with 40 dB SPL is constantly over 99% for all bigger intensities for bisyllabic lists and over 98% for monosyllabic lists, suggesting that the speech recognition is a little more difficult for monosyllabic words, in agreement with all well-known principles of speech recognition tests.

The presentation of words at intensities between 10 and 30 dB SPL presents the most variable results for this group of age, suggesting a wider variability of whisper understanding in the population with normal tonal hearing. It was realized the percent distribution of all subjects according to Word Recognition Scores categories for the two groups of tested lists.



a. Bisyllabic words lists (7_12.B) *b. Monosyllabic words lists (7_12.M)*

Figure I.1-3.8. Percent of the patients according to Word Recognition Score for all intensities.

For bisyllabic lists presented at 30 dB SPL over 70% of children understood 100% of words (figure I.1-3.8.a) and at 40 dB SPL over 97% present 100% intelligibility. As the level of presentation increases we can note a tendency for decrease of intelligibility (less than 100%), but still rest for all subjects between 90 and 99%. Scores below 89% are shown only at intensity levels less than 30 dB SPL.

For monosyllabic lists (figure I.1-3.8.b) the intensity level of presentation had to exceed 40 dB SPL to achieve the majority of subjects with 100% intelligibility (over 78%) and the rest between 90 and 99% (21%). We note two differences between monosyllabic and bisyllabic lists: the maximum of speech performance is present at 30 dB SPL for bisyllabic lists and at 40 dB SPL for monosyllabic lists and the intelligibility decreases slightly more for monosyllabic lists at 100 dB SPL intensity.

Discussions

The appropriate tests of speech perception performance in children should respect several criteria: the cognitive, motoric, and attentional demands of the test should be age-appropriate, performance should be independent of higher-level language abilities being appropriate to a linguistically common level, (Kosky, Boothroyd, 2003, Mendell, 2008). Creating a language corpus for primary school aged children based on early preschool education curriculum and primary school program approved by Ministry of Education and Scientific Research from Romania, we reached the goal of word familiarity and age-appropriate linguistic level. The absence of failure in speech recognition among the subjects as well as the absence of 100% for all children at more than 40 dB of presentation sustains the high quality of elaborated material.

The results of tested lists for each subject as well as for entire group for monosyllabic words and also for bisyllabic words show parameters that fit with the normal vocal audiogram slope. The variability of the responses for normal hearing children for this group of age allows

us to describe not just a regression line, but an area of the speech intelligibility audiogram that defines the normality. The methodology of developing the SRT materials was by selecting a subset of bisyllabic words with relatively steep psychometric function slopes and digitally equating their intensity to match the mean PTA of normally hearing subjects.

It is generally recognized the extreme difficulty, if not impossibility, to simulate the frequency of phoneme occurrence in a language with a list containing a limited number of words. (Nissen et al., 2011; Harris et al., 2007; Nissen et al., 2007). We realized phonetically balanced words list ensuring the test of subjects with the most common words of spoken language. Once validated for normal hearing for 7-12 years old, the tests can be applied in the audiological assessment of hearing loss in children, to evaluate the speech understanding for hearing aided or cochlear implanted children.

3. ***Research for teenagers and adults***

Results

The descriptive statistics of the study group indicated a predominance of females - 70.6% compared to males - 29.4% and an average age of the study group of 33.9 years. A significant number of list runs were performed for each category to ensure coverage of all test intensities within each word list: 998 runs for bisyllabic word lists, 535 runs for monosyllabic words, and 358 for logatome lists with a total of 1887 runs.

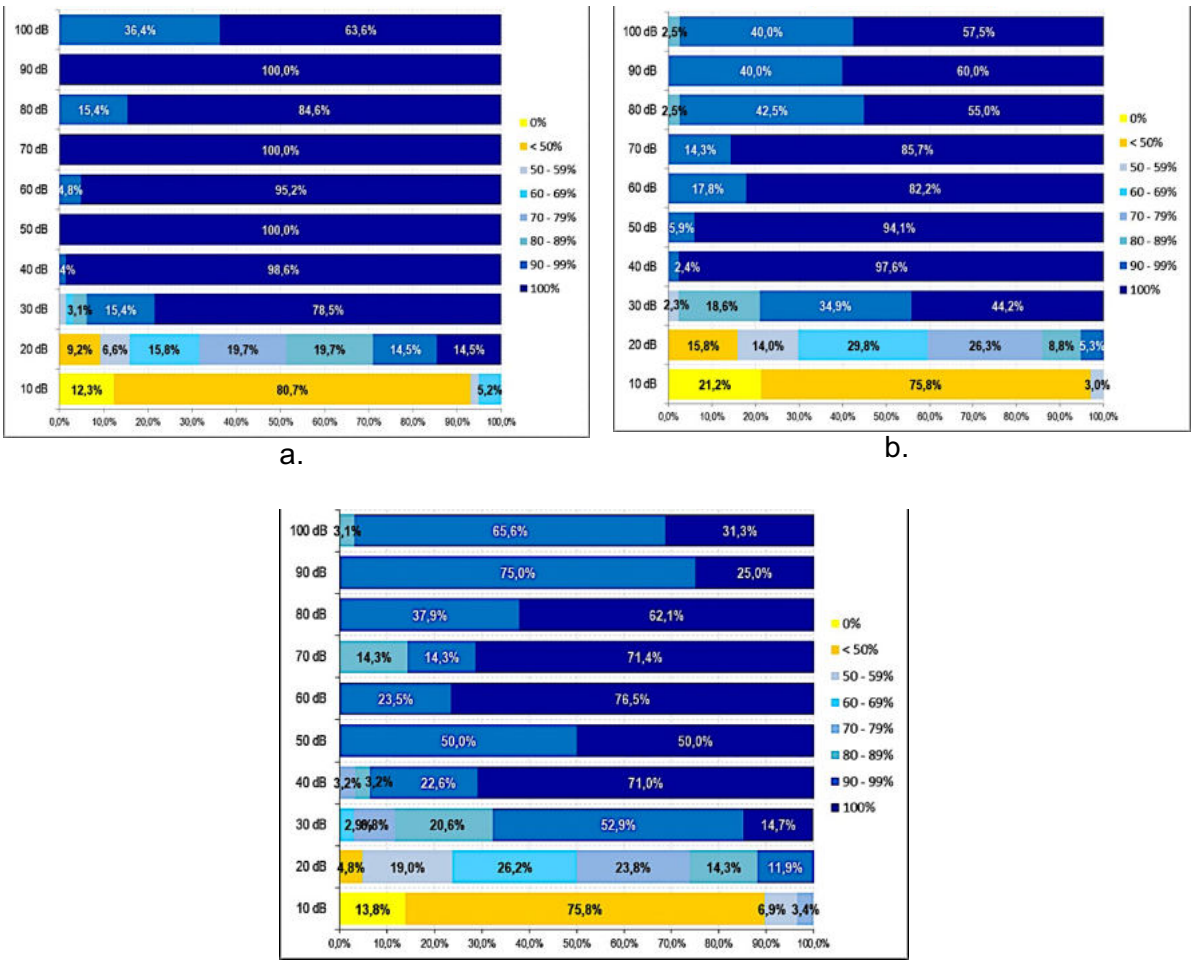
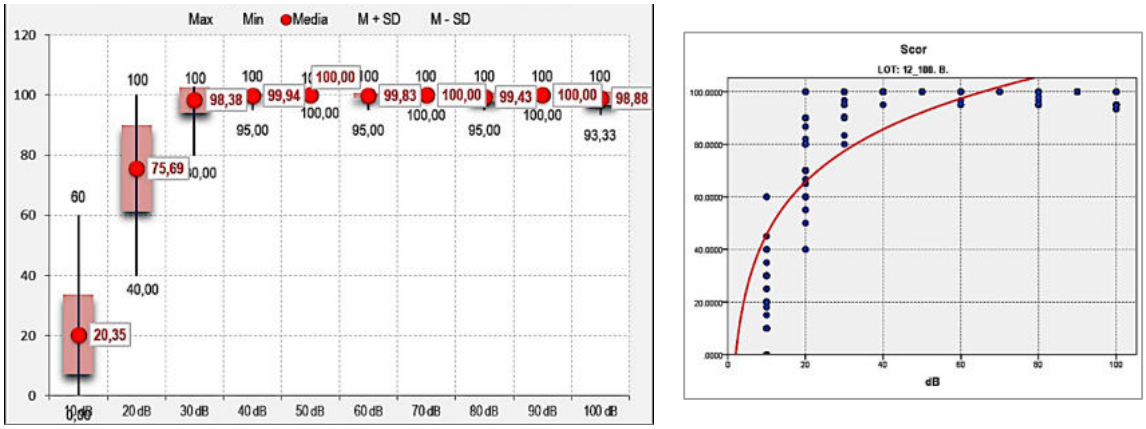


Figure I.1-3.9. Percent of the patients according to Word Recognition Score for all intensities:
a. Bisyllabic words lists - **12_100.B**
b. Monosyllabic words lists - **12_100.M**
c. logatome lists – **12_100.L**

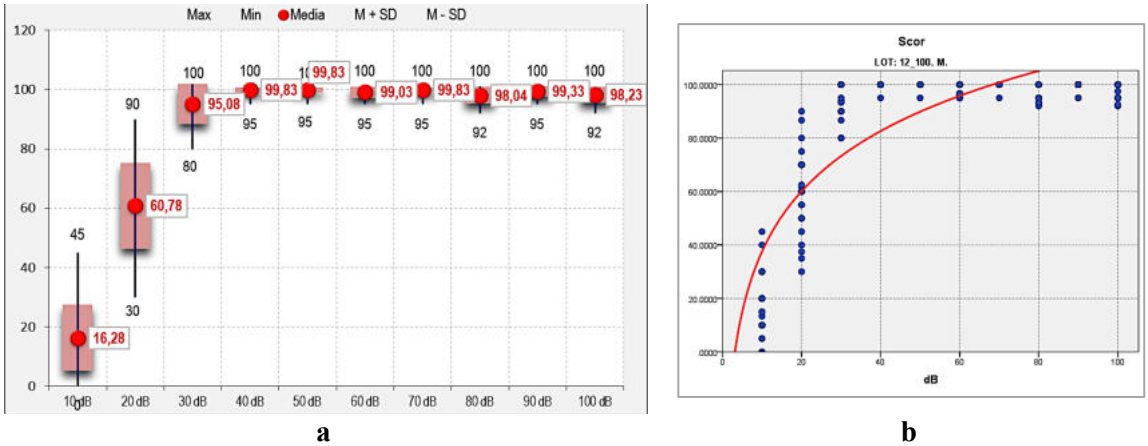
In all study conditions, it is observed from the graphical representation of the percentage of word recognition at different test intensities in figure I-3.9, that at the presentation intensity of over 40 dB SPL the recognition was between 90 and 100%, at the intensity of 10 dB SPL was below 50% for most subjects, with a small percentage of recognition above 50%, while for the intensity range 20-30 dB SPL are present different percentages of recognition in the group of patients, but respecting the tendency to increase the percentage recognition as the intensity of word list presentation increases. At the intensity of 40 dB SPL over 90% of the subjects recognized 100% of the presented words, with very high percentages of recognition in proportion of 100% at all intensities over 40 dB SPL. The intensity of 20 dB SPL shows the most varied percentages of word recognition. 12_100.L group presented the largest variations for the range 20 - 40 dB SPL.



a. **b.**

Figure I.1-3.10. a. Word Recognition Score (WRS) % for all intensities in **12_100.B group**
b. Graphical representation of the logarithmic estimation function for **12_100.B group**

For the group of patients 12_100.B it is observed from the graphical representation of the average voice recognition score for each intensity tested (figure I.1-3.10.a) a variation between 20.35% of the voice recognition score at 10 dB SPL, with an average score of 75, 68% at the intensity of 20 dB SPL and 98.38% at the intensity of 30 dB SPL; values very close to 100% of the word recognition score are observed starting with the intensity of 40 dB SPL.



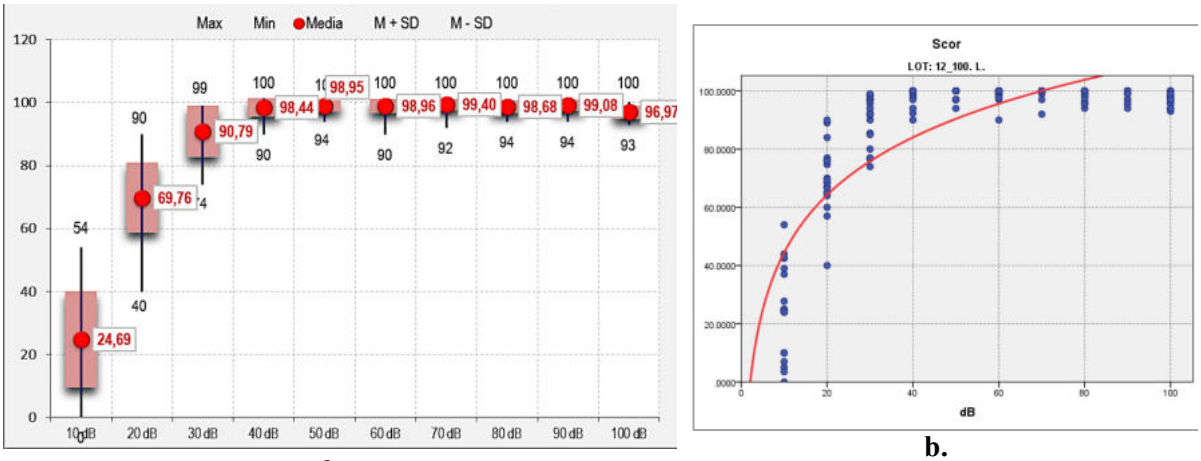
a **b**

Figure I.1-3.11. a. Word Recognition Score (WRS) % for all intensities in **12_100.M group**
b. Graphical representation of the logarithmic estimation function for **12_100.M group**

Based on the observation of the variations of the vocal recognition score in the 0 - 40 dB SPL interval within the study groups, the problem of avoiding the reporting of normality to a single vocal audiometric curve arises, the variation of vocal recognition in patients with normal hearing occurring in a range which is much more entitled to represent normalcy. Hence

the need to calculate for each group of patients a mathematical function that relates the normal to this function and also the variations from an average of the normal. Thus, by projecting on the graph of the vocal audiogram, a reference interval of the speech perception at normal hearing is obtained. Figure I.1-3.10.b shows the graphical representation of the logarithmic estimation function for 12_100.B group.

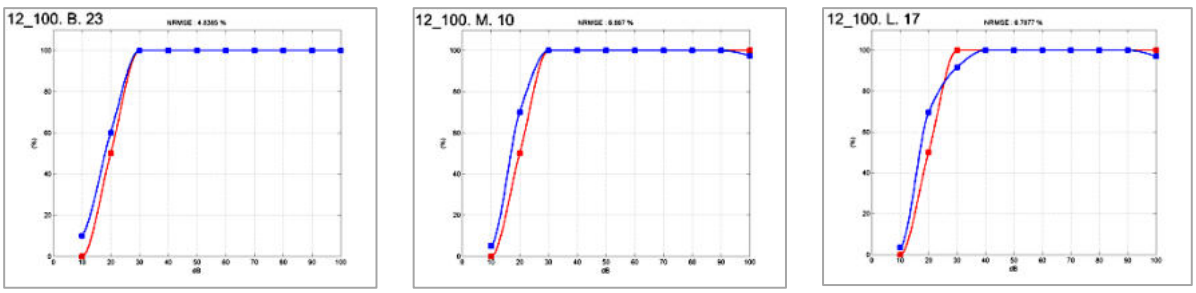
The graphical representation of the mean voice recognition score for each intensity tested for the 12_100.M patient group (figure I.1-3.11.a) shows an average voice recognition score of 16.28% at 10 dB SPL, an average score of 60.78% at intensity of 20 dB SPL and 95.08% at the intensity of 30 dB SPL; values very close to 100% of the word recognition score are observed starting with the intensity of 40 dB SPL. The graphical representation of the logarithmic estimation function for 12_100.M group is shown in figure I.1-3.11.b.



a. b.

Figure I.1-3.12. a. Word Recognition Score (WRS) % for all intensities in **12_100.L group**
b. Graphical representation of the logarithmic estimation function for **12_100.L group**

The graphical representation of the mean voice recognition score for each intensity tested for the 12_100.L patient group (figure I.1-3.12.a) indicates an average voice recognition score of 24.69% at 10 dB SPL, an average score of 69.76% at intensity of 20 dB SPL and 90.97% at the intensity of 30 dB SPL; also very close to 100% of the voice recognition score is observed starting with the intensity of 40 dB SPL. The logarithmic estimation function for 12_100.L group is plotted in figure I.1-3.12.b.



a. b. c.

Figure I.1-3.13. Graphical representation and NRMSE parameter values for randomly selected lists
a. **12_100.B.23 list**; b. **12_100.M.10 list**; c. **12_100.L.17 list**.

Statistical validation of each word list was performed in an original manner using a statistical parameter - Normalized Root Mean Square Error (NRMSE) calculated for each list (Taylor et al., 2016). This parameter determines the fitting degree of the curve obtained in testing with an ideal vocal audiometric curve commonly used in the literature and has been

calculated to verify that the list is valid or not (this parameter, expressed as a percentage, must be as small as possible). All lists in the test material were validated, and figure I.1-3.13 provides some examples of the graphical representation and values of the NRMSE parameter in the tested lists.

Conclusions

This is the first Romanian clinical validated test respecting all auditory test standards in terms of the homogeneity of the material: frequency of the words in the spoken language – communality factor; balanced frequencies spectrum representation similar to frequencies spectrum of common spoken language; known words corresponding to speech and cognitive specific age development, according to national preschool and primary school education curriculum. The originality of our work is that we realized phonetically balanced words list using our own and original algorithm ensuring the exposure of subjects to all frequencies spectrum of common Romanian spoken language. The study demonstrated that the tested material was homogenous; every single list of 10 words could be securely interchanged with any other one with the similar results in intelligibility performance. The material is comprehensive enough to provide a variability of the words in order to avoid a word repetition that could involve the cortical substitution based on the memorized previous presentation of the terms. Statistical analyses showed that for both bisyllabic and monosyllabic tests there are no significant statistically differences between results of different lists presentation for the same level of intensity among tested children. The results emphasize that the speech perception of the presented material is according to normality of normal hearing population.

The tests we developed represent an important validated tool to be used for all groups of age for assessment of hearing and communication common disorders as well as for other special hearing pathological conditions as auditory neuropathy spectrum disorders, neurological diseases or associated comorbidities with normal or subnormal tonal hearing and inappropriate speech recognition and production.

The battery of vocal tests that our team developed for the clinical audiological balance is being approved by OSIM (State Office for Inventions and Trademarks) Romania.

I.1.4. Special categories of hearing loss: contributions for diagnostic and evolution profile

I.1.4.1. Genetic diagnostic for inner ear pathology in Romanian population

Background

Hearing loss is one of the major public health problems, with a genetic etiology in more than 60% of cases. Connexin 26 and connexin 30 mutations are the most prevalent causes of deafness. Hearing loss (HL) is the most common sensory disorder in human, with an incidence at birth of 1 to 650 newborns (White, 2004, Smith et al., 2005) and a prevalence in the population of 10–12% (Adams, Benson, 1991, Mohr et al., 2000). Due to its high prevalence, HL is placed amongst the major public health problems, hence the need of screening programs development (White, Maxon, 1995, American Academy of Pediatrics, 2007).

The main purpose for early detection of children with HL is conventional hearing aid fitting or cochlear implantation at the right moment for optimal auditory and speech rehabilitation of the child (McPhillips, 2010). As known, rehabilitation results are mainly related to the cochlear implantation age (Houston, Miyamoto, 2010, Manrique et al., 2004), but also to other factors among which probably the HL etiology (Connell et al., 2007). HL can have a genetic cause, can be acquired or can be multifactorial (Parving, 1993).

Genetic deafness can be syndromic in 30% of cases (when it is associated with other pathologic findings) or nonsyndromic in 70– 80% of the total genetic deafness (Morzaria et al.,

2004) – when it appears isolated to a seemingly normal person. Genetic mutations responsible for HL cases can occur in autosomal or gonosomal chromosomes but also in mitochondrial DNA (Parving, 1993, Fischel-Ghodsian et al., 1997, Griffith, Friedman, 2006). The autosomal recessive forms represent about 80% of the total nonsyndromic deafness (Petersen, Willems, 2006), usually characterized by a sensorineural type involving the whole frequency range (Snoeckx et al., 2005). The DFNB1 locus on chromosome 13q11–12 is the most frequently affected one. Mutations located at this level are responsible for more than 50% of the autosomal recessive sensorineural hearing loss (ARSNHL) (Estivill et al., 1998). Two genes have been associated with the DFNB1 locus – GJB2 and GJB6 – involved in the auditory function by encoding the gap-junction proteins connexin 26 and connexin 30 (Kelley et al., 1999, Hilgert et al., 2009). Both connexins are components of the gap-junction channels that mediate electrolytic and other meta- bolites changes required for the inner ear function.

In the GJB2 gene there were 91 described mutations, out of which 89 with recessive features. The prevalence of each mutation is different from one population to another according to the founder effect theory (Nance, Kearsey, 2004, Van Laer et al., 2001). In the Caucasian population the most frequent mutation is c.35delG (approximately 2/3 of cases) (Van Laer et al., 2001, Gasparini et al., 2000). In the Asian population the c.235delC mutation is the most encountered (Ohtsuka et al., 2003, Abe et al., 2000, Liu et al., 2002), while in the Jewish population the most frequent mutation is c.167delT (Morell et al, 1998). The p.R143W mutation is predominant among certain Africans (Kudo et al., 2000) and the p.W24* mutation among European Gypsy and Indian people (RamShankar et al., 2003).

Mutations responsible for deafness can be monogenic (only one gene involved) or digenic (simultaneous involvement of 2 genes). Related to this, the role of GJB6 gene adjacent to GJB2 gene on the DFNB1 locus is described (del Castillo et al., 2005). The most frequent mutation in the GJB6 gene is a deletion – the 309-kb deletion (del Castillo et al., 2002). This deletion induces deafness either in homozygote form or in compound heterozygous form, in the last case only if there is a mutation at the level of the GJB2 gene on the pair chromosome. The prevalence of this deletion in the GJB6 gene is variable depending on the studied population (del Castillo et al., 2003).

Main published papers in this field:

- Rădulescu L, Mârţu C, Birkenhäger R, **Cozma S**, Ungureanu L, Laszig R. Prevalence of mutations located at the dfnb1 locus in a population of cochlear implanted children in eastern Romania. *International Journal Of Pediatric Otorhinolaryngology.* 2012; 76(1): 90-94. (IF=1,350).

Scientific contributions / Clinical implications:

- This study was the first report of this type in our country which characterize and establish the prevalence of the GJB2 and GJB6 gene mutations in a population of cochlear implanted recipients from Eastern Romania.
- The results represent a contribution to the scientific knowledge of genetic hearing loss and contribute to the existing international database by gathering the information necessary to establish the implications of connexin 26 mutations in auditory and speech rehabilitation in cochlear implanted recipients and to gather useful data necessary for the genetic counseling and for the genetic screening of deafness.

Aim of the study

All around the world significant efforts are being made to achieve the descriptive epidemiology related to connexin 26 mutations; in this regard, the main purpose of this study is to characterize and establish the prevalence of mutations at the level of the GJB2 gene, and to evaluate the prevalence of the deletions del(GJB6-D13S1830), del(GJB6-D13S1854) and del(chr13:19,837,343–19,968,698) in the GJB6 gene in a population of cochlear implanted recipients in Eastern Romania, which makes it the first study of this type in our country.

Materials and methods

The study was performed on 45 patients from Eastern Romania, 25 males and 20 females (unrelated to each other) evaluated, diagnosed and cochlear implanted in the Department of Otorhinolaryngology, Head and Neck Surgery, Clinical Rehabilitation Hospital, University of Medicine and Pharmacy ''Gr. T. Popa'' in Iasi, Romania. The Ethics Committee of the University of Freiburg approved this part of the project (no. 161/02-07/2003/Birkenha¨ - ger). The study was also approved by the Ethics Committee of the Clinical Rehabilitation Hospital Iaşi (no. 12511 – 10.07.2009). The evaluation protocol consisted of: medical history of the disease, especially regarding the onset modality and evolution of deafness, associated symptoms and their development, past personal and family medical history to exclude any possible family interrelations and other possible causes of deafness, complete ENT examination, complete audiologic assessement, speech therapist examination, imaging testing – CT and MRI. Also, interdisciplinary complex examination (ophthalmologic, pediatric, clinical genetic, psychiatric, etc.) was performed to exclude syndromic forms.

All patients included in this study were cochlear implant users for congenital nonsyndromic or early onset idiopathic progressive severe (71–90 dB) to profound (>90 dB) SNHL. All of them have worn conventional hearing aids for at least 6 months – without any benefits – before being implanted. All were unilaterally implanted when included in the study. In cases with asymmetrical HL, the most impaired ear was implanted.

Genomic DNA of patients was extracted from peripheral blood leukocytes of the patients using the standard methods (Qiagen, Hilden Germany). Primer and PCR conditşons were selected according to procedures optimized previously for sequence analysis of exon 1 and the coding exon 2 of the GJB2 gene, including all splice sites (Birkenhäger et al., 2006) and analysis of the GJB6 deletions del(GJB6-D13S1830), del(GJB6-D13S1854) and del(chr13:19,837,343–19,968,698) (Wilch et al., 2010). Sequencing of the PCR products was done with standard procedures and analyzed in an automated DNA sequencer Amersham MegaBACETM 500 (Amersham Biosciences, GE Healthcare Europe, Munchen, Germany). For the examination of the GJB6 gene (connexin 30) deletions the breakpoint junctions of del(GJB6-D13S1830) and del(GJB6- D13S1854) were analyzed according to del Castillo et al. (del Castillo et al., 2002, del Castillo et al., 2005), the deletion del(chr13:19,837,343–19,968,698) was analyzed according to Wilch et al. (Wilch et al., 2010).

Results

Our study included 45 cochlear implanted patients, 43 had bilateral congenital severe to profound SNHL and 2 had progressive HL that required cochlear implantation at ages of 6 and 8 years, respectively. The genetic analysis of the GJB2 (connexin 26) and GJB6 (connexin 30) genes identified in 22 (48.8%) patients mutations in the GJB2 gene: 12 (26.6%) patients were homozygous for the c.35delG mutation; 5 (11.1%) patients were compound heterozygous with c.35delG mutation on one allele and a different mutation on the other allele; 1 (2.2%) patient was compound heterozygous for two different mutations non c.35delG; in 4 (8.8%) patients only one mutated allele was identified (Table I.1-4.A).

Table I.1-4.A. GJB2 and GJB6 genotypes found in 22 subjects out of a collective of 45 patients with non-syndromic hearing loss

Compound homozygous	
c.35delG/c.35delG	12
Compound heterozygous	
c.35delG/c.313_326del14	2
c.35delG/c.71G>A	1
c.35delG/c.551G>C	2
c.71G>A/c.299_300delAT	1
Heterozygous affected	
wt/c.35delG	3
wt/c.358_360delGAG	1
Total mutated subjects	22
No mutation found	23
Total subjects	45

The analysis of 90 alleles revealed 6 different mutations, four of these alterations are truncating mutations, c.35delG, c.71G>A p.W24*, c.299_300delAT and c.313_326del14 (AAGTTCAT- CAAGGG), the two other alterations are non-truncating mutations, c.358_360delGAG p.delE120 is a in frame deletion and c.551G>C p.R184P is a missense mutation. The truncating mutation c.35delG represents 80% of all the mutated GJB2 (connexin 26) alleles, the prevalence of this mutation is 35.5% (32/90) in the investigated collective of patients all the mutations p.W24*, p.R184P and c.313_326del14 have a prevalence of 2.2% (2/90) and the mutations c.299_300delAT, and p.del E120 have a prevalence of 1.1% (1/90) (Table I.1-4.B).

The GJB6 (connexin 30) deletions GJB6-D13S1830, GJB6- D13S1854 and del(chr13:19,837,343–19,968,698) were not detected in our patients (Lerer et al., 2001, del Castillo 2002, 2005, Wilch et al., 2010). Additionally no polymorphisms were identified. Exon 1 was analyzed in all individuals who proved to be heterozygous for only one coding mutation, to identify the splice-site mutation IVS1+1G>A. Both patients with progressive SNHL were compound heterozygous (c.35delG + c.313_ 326del14 and c.35delG + c.71G>A p.W24*).

Table I.1-4.B. Spectrum of *GJB2* (Connexin 26) mutations detected in non-syndromic hearing loss in our group.

Nucleotide	Protein	Classification	Mutation type	No.	References
c.35delG	p.Gly12Valfs*2	T	Deletion/Nonsense	32	Denoyelle et al., 1997
c.71G>A.	p.Trp24* (p.W24*)	T	Nonsense	2	Kelsell et al., 1997
c.299_300delAT		T	Frameshift	1	Abe et al. (2000)
c.313_326del14	p.Lys105Glyfs*5	T	Deletion/Frameshift	2	Denoyelle et al., 1999
c.358_360delGAG	p.delGlu120 (del E120)	NT	In Frame Deletion	1	Denoyelle et al., 1999
c.551G>C	p.Arg184Pro (p.R184P)	NT	Missense	2	Denoyelle et al., 1997

T, Truncating mutation; NT, non-truncating mutation Total mutated alleles: 40

Discussion

The present study, like many others published in the recent years, describes the genetic mutations present on the DFNB1 locus in cochlear implanted recipients. Although, significant efforts have been made worldwide to define the epidemiology of GJB2 and GJB6 genes mutations related to HL, the issue remains open for some populations. This is the first report in Romania of the genetic profile of a group of cochlear implanted recipients with bilateral severe to profound SNHL due to mutations in the GJB2 and GJB6 genes.

A previous study, performed in the Northwest region of Romania, determined only the prevalence of two mutations (c.35delG and p.W24*) in the GJB2 gene, in non-cochlear implanted patients with different degrees of SNHL (Birkenhäger et al., 2006, Lazăr et al., 2010).

As our study enrolled only patients with idiopathic deafness, a large number of cases (40%) with genetic HL secondary to DFNB1 mutations were identified, which is consistent with the literature data according to which the GJB2 mutations are the most frequent cause of ARSNHL in most world populations, accounting for up to 50% of ARSNHL cases (Snoeckx et al., 2005). These findings emphasize the importance of GJB2 screening in our population for early detection of severe to profound hearing loss. The c.35delG mutation is most frequently occurring in the Caucasian populations and may account for up to 70% of all GJB2 mutations. As we had expected the most frequent mutation in our group was c.35delG in homozygote state present in 66.7% of the patients with GJB2 mutations. The second most common mutation (p.W24*) was found in compound heterozygous form in 2 of 18 patients with connexin 26 mutation on both alleles (Table I-4.A). This mutation is considered characteristic for the European Gypsy and Indian Population (RamShankar et al., 2003). These findings are similar with those reported by other authors for the Central and Eastern Europe (del Castillo et al., 2005, Frei et al., 2002, Toth et al., 2004, Uyguner et al., 2003, Minarik et al., 2003).

Four (8.9%) heterozygous patients were found, 3 (6.66%) for the c.35delG mutation and 1 (2.22%) for the c.358_360delGAG without any other alteration either on the GJB2 or GJB6 gene on the second allele. This cannot explain the hearing impairment of these patients (Ohtsuka et al., 2003). The etiology of deafness in these patients is possible to be secondary either to a nongenetic factor or to another mutation unrelated to DFNB1 locus and the affected patients can be carriers of GJB2 mutations. The fact that none of the patients included in the study had the GJB6 gene deletions, that we analyzed, implies that further studies on greater populational groups are necessary to evaluate the epidemiologic significance of these mutations in our country. The findings that the number of deaf persons carrying a single GJB2 mutation is higher than expected led to a search for other mutations in, or near GJB2. As a result there have been identified two large deletions: del(GJB6-D13S1830), del(GJB6-D13S1854) and the deletion del(chr13:19,837,343–19,968,698) (Wilch et al., 2010). These deletions truncate the neighboring GJB6 gene and inhibit the GJB2 gene expression (by deleting probably a GJB2 regulatory element not yet identified) so that they may be considered GJB2 mutations as well. Literature data shows that these mutations are usually found in compound heterozygosity with a GJB2 coding mutation causing significantly worse HL than most other GJB2 mutations (del Castillo et al., 2005).

One argument for this might be that the expression of both copies of GJB2 and one copy of GJB6 is abolished. The del(GJB6-D13S1830) deletion seems to be worldwide spread with a much higher occurrence rate than del(GJB6-D13S1854) – found mainly in Spain and the UK (del Castillo et al., 2005, Pallares-Ruiz et al., 2002). There are significant more GJB2 mutation carriers without any of these 2 deletions, indicating that other unidentified mutations/deletions may be present at the DFNB1 locus, or that another HL cause may be involved. As to the genotype–phenotype correlation, mention should be made of the fact that even if the literature states that HL caused by connexin 26 mutations is non evolutive (Snoeckx et al., 2005) – our group includes 2 patients with progressive idiopathic deafness, with early-onset. Progressive

hearing deterioration, up to the point where conven- tional hearing aids become useless (at ages of 6 and respectively 8 years in our group), requires cochlear implantation. The genetic profile of these patients was compound heterozygous in both cases (c.35delG + c.313_326del14 and c.35delG + c.71G>A p.W24*). However, nowadays, more and more authors report cases with SNHL with early-onset and progressive evolution in patients with connexin 26 mutations (Hochman et al., 2010, Pagarkar et al., 2006). No possible correlation could be established between deafness degree and genotype, because the studied group consists only of patients with severe to profound SNHL that were cochlear implanted. At individual level, knowing the genetic etiology is essential for the genetic counseling. There is a 25% recurrence chance for parents that have one child with GJB2-related deafness to have another child with the same genotype. Also there is a 66% chance that the second child will have mild-to-moderate HL and a 34% chance that the HL will be more severe if their first child has mild- to-moderate HL. Furthermore, progress made in characterization of genotype–phenotype correlations allows appropriate informing regarding prognostic implications. Several studies have shown that in such a child with severe-to-profound HL that receives a cochlear implant, the parents can expect their child to have an excellent outcome (Connell et al., 2007). A genetic diagnosis can be beneficial to parents preventing sometimes parental guilt and anxiety (Connell et al., 2007, Denoyelle et al., 1999).

Conclusions

The genetic analysis of GJB2 mutations revealed that 48.8% of cochlear implanted patients present mutations of connexin 26. We found an important number of different mutations (6 different mutations) with implications in hearing screening programs development in eastern Romania. The most prevalent mutation of GJB2 gene was c.35delG mutation. We did not find any new mutation. The connexin 30 studied deletions were not detected in our group.

Other papers in this field:

- Meriacre Tatiana, Birkenhaeger Ralph, Chiaburu-Chiosa Doina, **Cozma Sebastian**, Rusu Cristina, Popescu Roxana, Gavril Eva, Resmerita Irina. Genetic Screening of Gjb2 Gene in Romanian Congenital Severe to Profound Non-Syndromic Deafness. *Proceedings of 5th Medical Genetics Congress with International Participation.* 2018: 164-168.
- Butnaru Corina, Meriacre Tatiana, Cumpata Adeline, Cobzeanu Bogdan, **Cozma Sebastian**, Necula Violeta, Martu Cristian, Birkenhäger Ralf. Sensorial Hearing Loss Secondary to GJB2 Mutation**.** *Proceedings of National Romanian ENT, Head and Neck Surgery Conference.* 2018: 107-110.

Scientific contributions /Clinical implications:

- The knowledge of the prevalence of mutations in our population allows the development of adjusted screening programs. Our studies described the most frequent mutation in the GJB2 gene in children with severe and profound deafness in Romania. A total of 21 different mutations in *GJB2* gene were found in a population with non-syndromic congenital severe to profound hearing loss (NSHL) patients. The 35delG was the most common form of mutation that was present in 162 out of 251 (64.54%) mutated alleles. The next frequent type of mutation was c.71G>A, accounting for 24 out of 251 (9.56%) mutated alleles.
- Mapping the genetic mutations in the deaf population of Romania is useful in early treatment (with CI for example) but also in predicting individual outcomes after optimal treatment.

I.1.4.2. Hearing loss characteristics in evolution of the auditory neuropathy spectrum disorders (ANSD) in neonates and small children

Background

A new specific type of hearing loss was first described and titled ANSD (AN) by Starr in 1996 (Starr et al., 1996). Since 2000 the disease was define as auditory neuropathy spectrum disorder (ANSD) (Berlin et al., 2001) describing a condition in which a patient's otoacoustic emissions (OAE) are (or were at one time) present, and auditory brainstem responses (ABR) are abnormal or absent. Sometimes, ANSD is diagnosed on the basis of present cochlear microphonics (CM) and abnormal or absent ABRs with or without abnormalities of OAEs (Berlin et al., 1993, Rance et al., 1999). The ANSD is present in the well newborns, without risk (between 0.006% and 0.03%) (Korver et al., 2012), but the highest incidence was reported in newborn at risk (5.1%) (Bielecki et al., 2012). The most common risk factors are ototoxic medications, premature birth, low birth weight, and intensive care in excess of 7 days (Bielecki et al., 2011). Recent studies show that ANSD may be present in 10–15% of infants with sensorineural hearing loss (Roush et al., 2011). The site of lesion in AN is thought to be at the level of the inner hair cells, the synapse between the inner hair cells and the VIII nerve, or the VIII nerve, or any combination between these conditions (Berlin et al., 2001). The disappearance of otoacoustic emissions in some of the patients is confirmed in many studies in some patients with ANSD, but there are no data about the incidence rate of such disappearance (Talaat et al., 2013). Due to particular aspects in children with auditory neuropathy spectrum disorders consisting in the degree and evolution of hearing loss, audiometric configuration, speech perception and hearing aid benefit (Mathai, 2018, Narne et al., 2016, Mathai, Yathiraj, 2013, 2017, Yuvaraj, Mannarukrishnaiah, 2016), there is not yet a consensus in the therapeutic recommendation in newborns with auditory neuropathy (Narne et al., 2014, Ngo et al., 2006, Jiang, 2014). In 2015 we obtained through a competition the funding of the grant "Optimal therapy protocols for deaf newborns with auditory neuropathy studying electroneural and audiological dynamic progress during the stimulation by conventional hearing aid and cochlear implant", internal grant of the University of Medicine and Pharmacy "Grigore T. Popa" Iași. Within this grant, we had the opportunity to carry out a research project on auditory neuropathies, a representative article being presented in the following.

Main papers in this field:

- **Sebastian Cozma**, Oana Bitere, Cristian Martu, Raluca Olariu, Luminița Rădulescu. Evolution of hearing loss in children with auditory neuropathy spectrum disorders identified by neonatal hearing screening. *ORL.ro.* 2018; 41(4): 18-22. ISSN 2067-6530

Scientific contributions / Clinical implications:

- For the first time in Romania our team made a study of the special category of hearing loss - auditory neuropathy. We observed and described the evolution of early diagnosed hearing loss in children with neonatal auditory neuropathy spectrum disorders identified by universal neonatal hearing screening.
- Our results were obtained in a study grant of the University of Medicine and Pharmacy Grigore T. Popa Iasi and were presented with success in different international meetings: "Optimal therapy protocols for deaf newborns with auditory neuropathy studying electroneural and audiological dynamic progress during the stimulation by conventional hearing aid and cochlear implant"

Purpose of the study

The objectives of the current study are: to report our ANSD cases resulting from neonatal hearing screening, to identify and to describe specific patterns of hearing dynamic progress and speech development evolution in ANSD cases diagnosed immediately after our hearing neonatal screening.

Materials and methods

The study included all babies referred from maternities and diagnosed with auditory neuropathy in the Audiology Department of Rehabilitation Clinical Hospital Iași, Romania, in the last six years. In this period, within the universal auditory newborn screening program in maternities there were tested over 50,000 babies and, after the clinical audiological assessments in the audiology department, we identified and managed newborns with auditory neuropathy spectrum disorders. ANSD cases were diagnosed on the base of the following clinical criteria: the presence of otoacoustic emissions (at least at birth) and/or abnormal or absent ABR responses, the presence of cochlear microphonics and/or abnormal or absent ABR (auditory brainstem response), mismatches between ABR thresholds and ASSR (auditory steady state response) results or free field behavioral auditory thresholds (Cozma et al., 2015, Starr et al., 1996, Berlin et al., 2010, Lalayants et al., 2018). The follow-up was done for each child periodically until 18 months (at least three clinical evaluations) for cases fitted by hearing aids and until the cochlear im- plantation surgery for cases with this indication.

The follow-up of ANSD cases included: auditory assessment periodic control (every three or four months), including ASSR, ABR (rarefaction and condensation polarity), free-field behavioral audiometry, tympanometry, otoacoustic emissions, free-field behavioral audiometry with hearing aids or cochlear implant; periodic reports from speech therapy specialist (describing performances with hearing aids or with cochlear implant) regarding tonal perception, message intelligibility according to age and the level of speech production.

Results and discussion

The development of universal auditory newborn screening program allowed us to test in the Department of Audiology 1034 newborns sent from maternities for otoacoustic emissions test and/or for the presence of one or more risk factors. We finally identified 26 children (3%) with auditory neuropathy spectrum disorders (Figure I.1-4.1).

Figure I.1-4.2 shows the number of newborns identified by audiological testing during 2012 and 2016 in the first clinical phase.

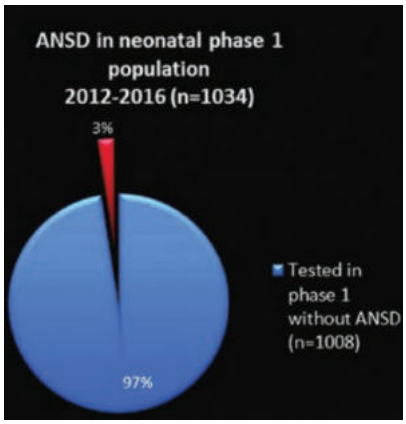


Figure I.1-4.1. Prevalence of ANSD in the hearing screened neonatal population referred to clinical audiologic assessment

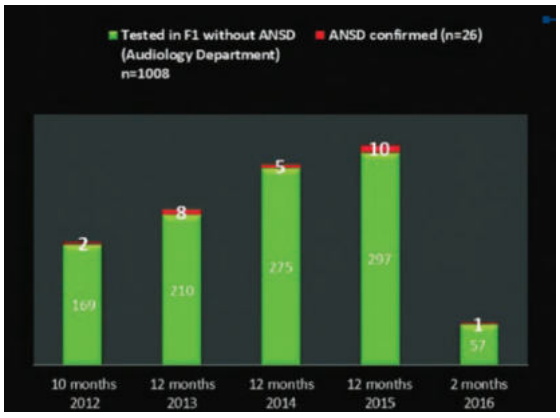


Figure I.1-4.2. Annual prevalence of ANSD in the hearing screened neonatal population referred to clinical audiologic assessment

In our study there were diagnosed six babies with ANSD, presenting normal tonal hearing, and 20 cases were diagnosed with different degrees of hearing loss (Figure I.1-4.3). In the group of children with hearing loss, we observed that seven children showed progressive forms, three presented fluctuating forms and ten children showed stable forms (Figure I.1-4.4).

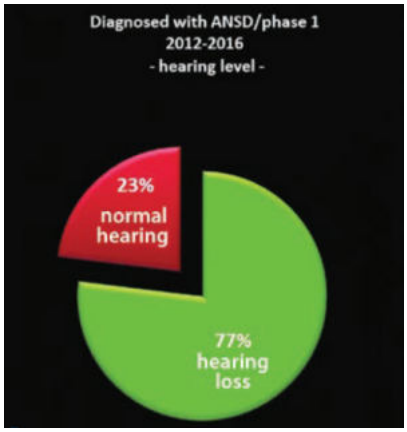


Figure I.1-4.3. Report of normal hearing versus hearing loss in children with ANSD

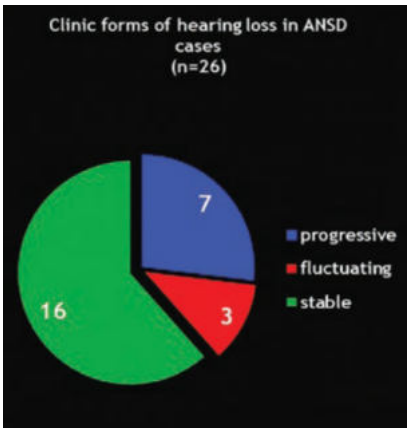


Figure I.1-4.4. Evolutive clinical forms of hearing loss in ANSD cases

All six cases of ANSD with normal hearing, according to the results of our follow-up process, conserved their auditory thresholds. In four cases, speech development cannot be appreciated yet (age between 8 and 15 months). In other two cases that did not develop speech production, one case showed evidence of a good evolution (Figure I.1-4.5).

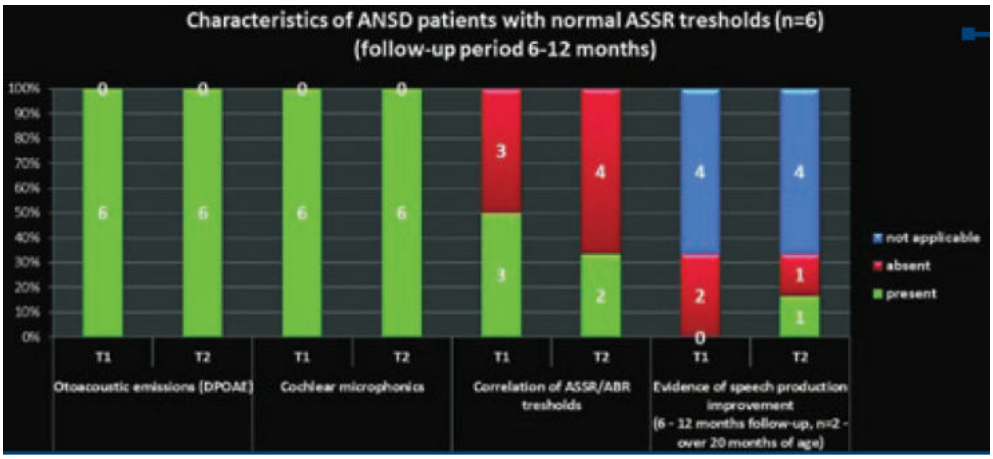


Figure I.1-4.5. Characteristics of ANSD patients with normal tonal hearing

An example of a newborn with ANSD and normal hearing is presented in Figure I.1-4.6, where we can observe the presence of cochlear microphonics even 8 months later than the diagnosis moment. All deaf children were hearing aid fitted, except for those with profound hearing loss with direct indication for cochlear implantation. For mild/moderate/severe hearing loss we used the hearing aids as the first choice. At the follow-up, when we found stable hearing loss thresholds with evidence of auditory gain and good speech development, hearing aids remained the best solution, with a periodic follow-up. When we identified a progressive hearing loss (proved after hearing aid fitted), we recommended unilateral cochlear implantation (the existence of a low speech development rate was not an argument against the evidence of hearing loss progressivity).

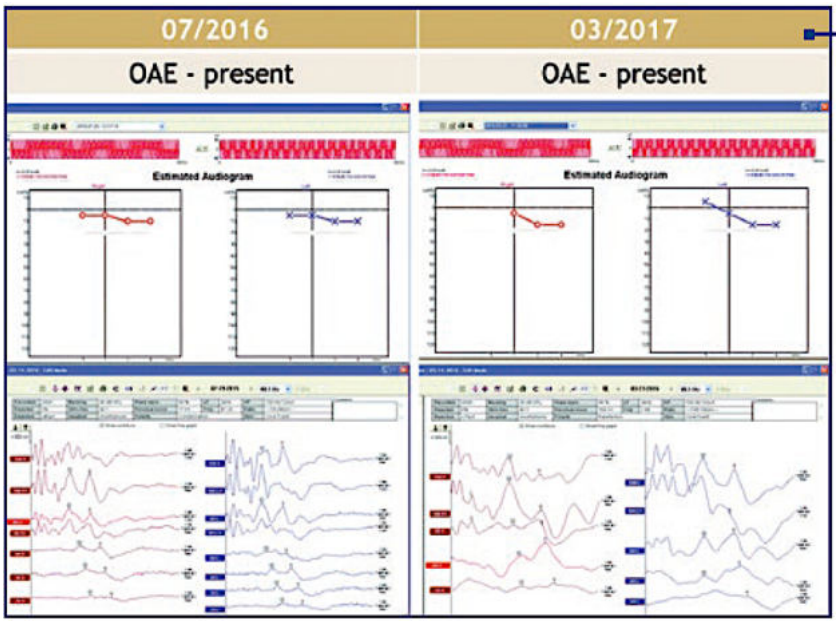


Figure I.1-4.6. ASSR and ABR response of a normal hearing ANSD child

In the group of children with hearing loss, we observed three cases with fluctuating hearing loss (Figure I.1-4.7 represents the fluctuations in ASSR thresholds level in a case with auditory neuropathy). For these children, the evaluation of the limits of fluctuation determined some difficulties for hearing aid fitting, and the evaluation of speech development showed us no evidences of good evolution. Depending on the available time or age of the patient, our indication was for unilateral cochlear implant. In our group, we did not find reversible hearing loss cases.

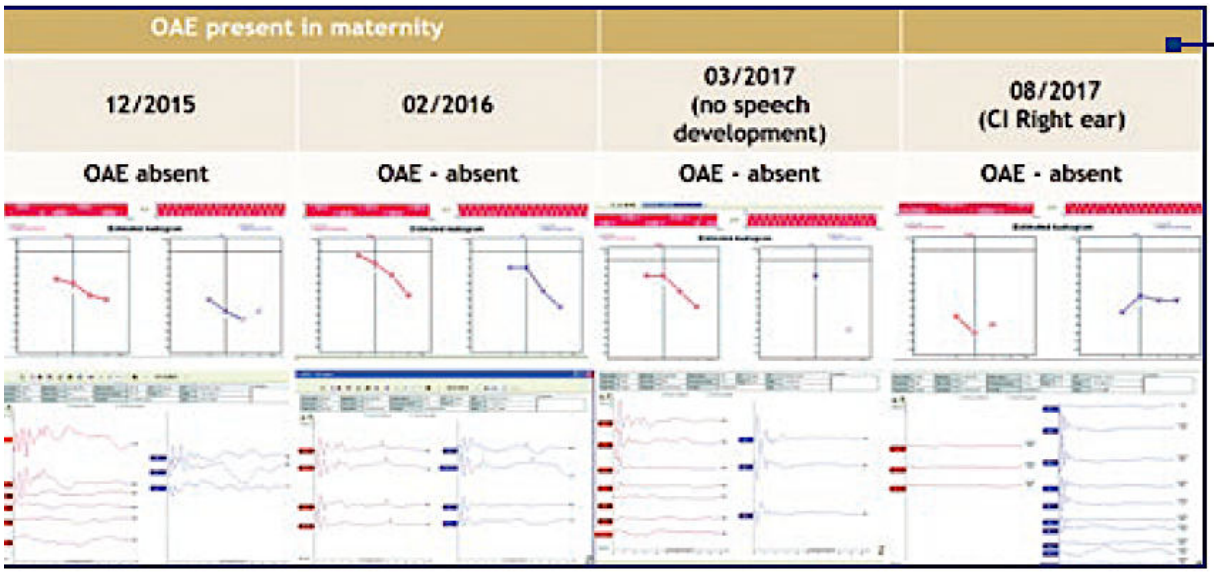


Figure I.1-4.7. Evolution of ASSR, ABR and OEA in a child with progressive/fluctuating ANSD

In the group of progressive hearing loss, 57% (9 cases) evolved under acoustic stimulation by hearing aids to profound deafness and cochlear implant indication (Figure I.1-4.8, Figure I.1-4.9). The greater the initial diagnosed degree of hearing loss, the children have more progressed to profound deafness.

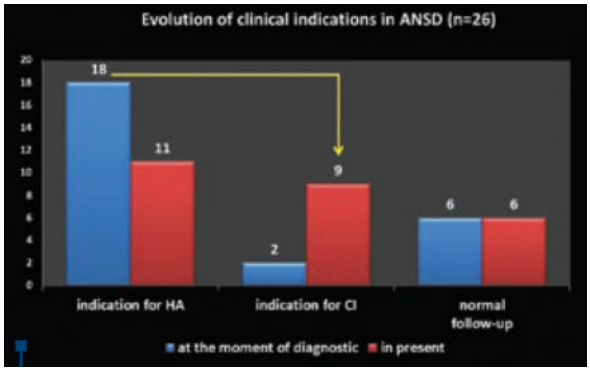


Figure I.1-4.8. Hearing dynamic progress evolution under acoustic stimulation

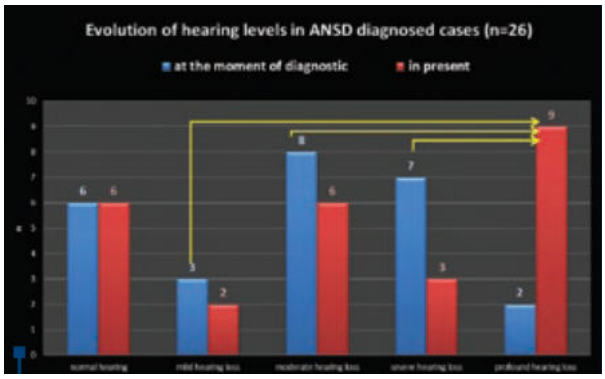


Figure I.1-4.9. Evolution of clinical indications based on hearing dynamic progress evolution under acoustic stimulation

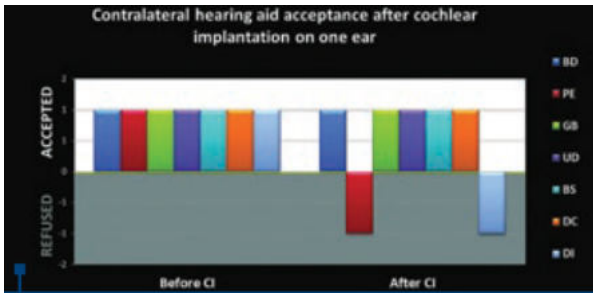


Figure I.1-4.10. Contralateral hearing aid acceptance after unilateral cochlear implantation

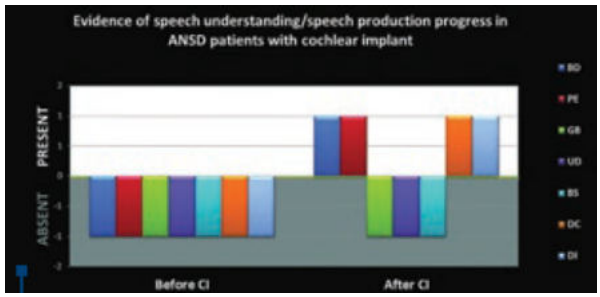


Figure I.1-4.11. Evidence of speech understanding/production progress in ANSD patients with cochlear implant

In cases with bimodal stimulation, two patients refused the contralateral hearing aid after few months from the switch-on of their cochlear implant. They are included among patients with evidence of good performances in speech development (Figure I.1-4.10).

Two patients with cochlear implant indication refused the surgery and they are still hearing aid users, with no evidence of speech development (Figure I.1-4.11). Four out of seven of cochlear implanted children showed evidence of good speech development until now – following survey is necessary. Patients with ANSD fitted by hearing aid without cochlear implant indication present different levels of progress in speech understanding and production.

Conclusions

Universal hearing screening in newborns offers the chance to identify children with auditory neuropathy, requiring a different diagnosis and therapeutic approach compared to patients with regular inner ear hearing loss. Auditory neuropathy spectrum disorders cannot be diagnosed only on the base of screening auditory tests in ma- ternity; the presence of different hearing loss risk factors is an important argument to indicate clinical audiological tests. ANSD was found in 3% of the newborns referred to our audiology department for clinical audiological tests (risk factors or "refer" result in screening tests), 23% presented normal tonal hearing and 77% presented different levels of hearing loss. We found different clinical forms of hearing loss: stable hearing level (16 cases), progressive hearing level (seven cases) and fluctuating hearing level (three cases). Because 35% of the patients with progressing hearing level switched from different degrees of hearing level to the profound one, we consider the periodical follow-up essential in the first 18 months in order to offer the best medical indication and to avoid the delay of appropriate intervention for hearing rehabilitation and speech development.

Note

The coordination of the grant "Optimal therapy protocols for deaf newborns with auditory neuropathy studying electroneural and audiological dynamic progress during stimulation by conventional hearing aid and cochlear implant" and my involvement in knowledge and researching current aspects of this special pathology, allowed the team I worked with to this grant to deepen the subject and to be able to communicate the results of our research at a multitude of national and international conferences and congresses, where we participated in poster sessions or oral presentations.

Other papers and communications in this field:

- **Sebastian Cozma**, Oana Bitere, Luminița Păduraru, Maria Stamatin, Raluca Olariu, Cristian Mârțu, Luminița Rădulescu (oral presentation, abstract published DBI). Incidence of auditory neuropathy in auditory screening in newborns**.** The Second National Congress of Pediatric ENT with international participation, Iași, 18-21 May 2016. *ORL.ro.* 2016; 31 (2): 50). ISSN: 2067-6530
- **Sebastian Cozma**, Cristian Martu, Oana Manolache, Maria Stamatin, Luminita Paduraru, Dan Martu, Raluca Olariu, Luminita Radulescu (oral presentation). Detection and management of auditory neuropathy in newborns: a challenge for the universal neonatal hearing screening. 13th International Congress of the European Society of Pediatric Otorhinolaryngology. 18-21 June 2016, Lisbon, Portugal and National Congress of Otorhinolaryngology and Cervico-Facial Surgery with International Participation, 19-22 October 2016, Oradea, Romania.
- **Sebastian Cozma**, Oana Bitere, Cristian Martu, Raluca Olariu, Maria Stamatin, Luminita Paduraru, Luminita Radulescu (poster). Auditory neuropathy spectrum disorders in children from neonatal hearing screening: hearing dynamic progress under acoustic or electric stimulation. 33rd World Congress of Audiology 2016, Vancouver, Canada, 18-21 September 2016 and 14th European Balkan Congress, Split, Croatia, 13-15 October 2016.
- **Sebastian Cozma**, Cristian Mârțu, Oana Manolache, Dan Mârțu, Cristina Hera, Luminița Rădulescu (oral presentation). The child with auditory neuropathy - a particular condition in the indication of the cochlear implant. National Congress of Otorhinolaryngology and Cervico-Facial Surgery with International Participation - 19-22 October 2016, Oradea, Romania.
- **Sebastian Cozma**, Oana Bitere, Cristian Martu, Raluca Olariu, Maria Stamatin, Luminita Paduraru, Luminita Radulescu (oral presentation). The auditory neuropathies spectrum disorders in children from neonatal auditory screening: dynamic auditory progress under acoustic or electrical stimulation. National Conference of ENT and Cervico-Facial Surgery, Sibiu, Romania, 17-20 May 2017.
- **Sebastian Cozma**, Cristian Martu, Oana Bitere, Raluca Olariu, Cristina Hera, Luminita Radulescu (poster). Cochlear Implant Indication Related To Auditory Neuropathy Spectrum Disorders Patterns. 15th Symposium on Cochlear Implants in Children, San Francisco, USA, 26-29 July 2017.
- **Sebastian Cozma**, Oana Bitere, Cristian Martu, Raluca Olariu, Cristina Hera, Raluca Lupescu, Luminita Radulescu - (e-poster). Evolution of Hearing Loss in Children with Auditory Neuropathy Spectrum Disorders Identified by Neonatal Hearing Screening. IFOS - ENT World Congress, Paris, France, 24-28 June 2017.

I.2. RESEARCH ON HEARING LOSS TREATMENT BY AUDITORY IMPLANTABLE DEVICES

Background

Disabling hearing loss (deafness) has, according to an estimate based on 42 population studies, a worldwide prevalence of 5,3%; 91% of those affected are adults, and the remaining 9% are children (WHO, 2012, Stevens et al., 2013). Also according to the WHO, disabling deafness is defined as an increase in hearing threshold over 40 dB in the best ear in adults (over 15 years) and over 30 dB in children (under 15 years). As a consequence of prelingual hearing loss in children, disorders in language development and cognitive disorders occur, and later decreased school performance (Fitzpatrick, 2015). In adults, hearing loss causes social isolation and difficulties in keeping a job (Rydberg et al., 2010).

For lesions located in the middle ear: discontinuity of the ossicular chain or tympanic membrane perforations, an attempt is made to perform a tympanoplasty or a stapedotomy in the case of otospongiosis. Achieving a tympanoplasty often involves the use of passive middle ear implants. Implant means any device that, placed in a surgically or naturally-formed cavity of the body, remains there for at least 30 days (according to FDA).

The failure of tympanoplasty requires the use of other methods of auditory rehabilitation. In the first line is the use of conventional hearing aids. Despite the negative consequences of deafness, only one in five people use conventional hearing aids (World Health Organization, 2006). The reasons why patients refuse to use them are: lack of benefit in the noisy environment, poor sound quality, inadequate adjustment with the degree of hearing loss, acoustic feedback, etc. (McCormack, Fortnum, 2013, Zenner, Leysieffer, 1997, Backous, Duke, 2006, Haynes et al., 2009). Situations in which the benefit with hearing aids is limited (under the conditions of a correct adaptation of the prosthesis and adequate patient counseling) or in situations where conventional prostheses are for various reasons unusable have led to the development of new devices: active middle ear implants (AMEI), cochlear implants (Ci), as well as bone anchored hearing aids (BAHA) (Zenner, Leysieffer, 1997, Backous, Duke, 2006, Haynes et al., 2009).

Main articles published in this field:

- Luminita Radulescu, Cristian Martu, Dan Martu, Gabriela Damean, **Sebastian Cozma**. The Hearing Loss: Indications for Implantable Hearing Devices. *ORL.ro.* 2015; 27 (2): 22-25. ISSN 2067-6530

Scientific contributions /Clinical implications:

- The treatment of deafness through implantable devices of middle ear and cochlear implant within the national program in Romania required the study of international protocols and their adaptation to the reality of our country, and the realization and publication of a review on this topic was expected to standardize deafness treatment solutions.

Active middle ear implants. The functioning of the AMEI is dependent on the use of an external energy source, which with the help of the implant is transformed into mechanical energy and is then transmitted directly to the ossicular chain or cochlea (Backous, Duke, 2006). AMEIs are either totally or partially implantable, using different modes of transduction of electrical energy into mechanical energy: piezoelectric or electromagnetic systems with its electromechanical variant (Haynes et al., 2009).

The main indication is for patients who cannot wear olives of conventional hearing aids (atresia or stenosis of the external ear canal, chronic otitis externa, allergy to the material from which the olives are made, etc.) as well as patients for whom acoustic feedback cannot be resolved. Each type of AMEI finds its indications according to specific audiological criteria. The benefits of AMEI are: achieving proper amplification, absence of acoustic feedback, increased ability to discriminate speech, external auditory canal is kept free (Manrique et al., 2008, Bouccara et al., 2005).

Bone-anchored hearing systems. Bone-anchored hearing implants realizes the transmission of the sound wave by bone to the cochlea by direct stimulation of the bone in which they are fixed (Haynes et al., 2009). Indications for this type of prosthesis are: mixed hearing loss or transmission hearing loss in which ossicular reconstruction could not be performed, the existence of large mastoid highlighting cavities, atresia or stenosis of the external auditory canal (EAC) or the existence of other conditions of the external auditory canal that do not allow wearing conventional prostheses only if the bone conduction is better than 65 dB (Bouccara et al., 2005, Amonoo-Kuofi et al., 2015). Another distinct indication is unilateral deafness, in which auditory information from the deficient ear is transmitted contralaterally by bone. (Haynes et al., 2009, Manrique et al., 2008, Bouccara et al., 2005, Amonoo-Kuofi et al., 2015, Lekue et al., 2013).

Cochlear implant. The cochlear implant is the first connection between man and an electronic device integrated in his body, hearing being so far the only sense that can be substituted. If in 1980 single-channel implants only allowed the detection of sounds and helped lipreading, today with the help of modern implants the implanted people can understand speech and can even use the phone (Bouccara et al., 2005, House 1976).

In the indication for cochlear implantation, audiological criteria are of major importance. The difficulty of performing and interpreting behavioral tests in children as well as the lack of objective tests that cover the entire range of frequencies, make the audiological criteria different in children.

Among the candidates for implantation are excluded people with acute or chronic inflammatory diseases of the middle and external ear. Healing the otic inflammatory process allows the inclusion of patients on the list of candidates for CI. Other contraindications to cochlear implantation are: absence of cochlea, absence of auditory nerve, ossified cochlea etc.

After the medical examination, the cause of deafness will be established, which may have implications for the cochlear implantation, such as:

- in case of temporal bone fractures, the facial nerve can be stimulated when the implant is activated, which requires the modification of the processing program;
- postmeningitis ossification of the cochlea modifies the implant procedure;
- type II neurofibromatosis requires auditory brainstem implant.

Age is not an impediment for CI. Currently, the lower limit has been reduced to 12 months, and at the other extreme, people aged 84-86 have been implanted, although usually the upper limit is 65 years (Deggouj et al., 2007, Sampaio et al., 2011). The indications for the cochlear implant in the child have undergone a profound transformation over time (Nicholas, Geers, 2007, Vincenti et al., 2014, Hang et al., 2012). If in the 1970s only adults were accepted for implantation, today children are mostly implanted. The candidate must be in a state of health that allows him to undergo general anesthesia (although CI was performed under local anesthesia) and surgery for 2-4 hours. The following are competing for successs of the implantation: the patient's motivation, family or entourage support, living and working conditions and, last but not least, the person's intelligence quotient.

The current indications refer to bilateral cochlear implantation, especially for cases of post-meningitis sensorineural hearing loss. Bilateral cochlear implantation is thought to improve sound localization and speech discrimination in noise and to remove the mask effect

of the head (Härkönen et al., 2015, Kan, Litovsky, 2015). Specifying the optimal moment for the second implantation in the child: simultaneously or sequentially? and if sequentially, then what is the critical period of completion of the second implantation? - remain to be determined (Peters et al., 2007, Kim et al., 2013, Gordon, Papsin, 2009).

Hybrid CIs (implants that combine electrical stimulation - for high frequencies and acoustic stimulation - for low frequencies) have emerged as a consequence of the need to improve the hearing of patients with partial hearing loss (Woodson et al., 2010).

The use of CI in unilateral deafness is gaining more and more followers. Studies comparing CI with traditional methods used in the treatment of unilateral deafness (CROSS system) recommend CI as an effective therapy (Blasco, Redleaf, 2014). Moreover, most studies on this topic emphasize the role of electrical stimulation on tinnitus, suppression in most cases 46-95% but also worsening in 5.6% of cases (Todt et al., 2015, Olze, 2015).

Auditory neuropathy (AN) comprises a heterogeneous group of diseases with an incidence of 2,4-15% of children diagnosed with sensorineural hearing loss (Hang et al., 2012, Roush et al., 2011). A study of 260 children diagnosed with An shows that 5% of these children developed normal language without the need for a hearing aid (Berlin et al., 2010). The results obtained after cochlear implantation in children with auditory neuropathy are variable (Teagle et al., 2010). More and more authors recommend the individual assessment of each case in an attempt to determine as accurately as possible the type and location of the lesion that causes the hearing loss. Electrocochleography and MRI are key explorations in predicting positive postimplant results.

Conclusions

Implantable hearing aids have emerged as a necessity for cases where medical or surgical treatment is not appropriate or failed as well as for cases where the patient does not benefit or cannot wear conventional hearing aids for various reasons. This paper presents the solutions of implantable prostheses of middle and inner ear, from the classical indications, following in time their evolution to the present time, as well as trends in the extension of indications, trends that appear with technological development and improvement of surgical technique. Today we are discussing the extension of the indications for cochlear implantation, outlining more and more the principle according to which cochlear implantation aims to obtain a postimplant hearing benefit that is better than the benefit obtained by using conventional hearing aids.

I.2.1. The study of the auditory electro-neural loop – basic functional structure in cochlear implant stimulation

Background

Technological development in cochlear implant is mainly concerned with gathering objective information that is used to assess the technical condition of the implant over time, but more than this it can be an important reference point to guide clinicians in controlling the implant especially when dealing with children.

These are the most objective electrophysiological tests which are currently available:

- telemetric impedancemetry;

- recording the electrically evoked compound action potential in cochlear nerve - ECAP (electrically evoked compound action potential) as characteristic of each device: Nucleus - NRT (neural response telemetry), Medel - ART (auditory response telemetry), Advanced Bionics - NRI (neural response imaging);

- observing the stapedius reflex by electrical evocation and measurement of electrical occurrence frequency;

- performing auditory evoked electrical potential (recording the evoked potentials after electrical stimulation through implant (Dillier et al., 2002).

These tests can be performed both intraoperatively and postoperatively; none of the methods being invasive, measurements can be repeated as many times as it is needed.

Telemetry represents a bidirectional communication system (Neihart, Harrison, 2005). The exterior communicates with the inside part allowing the system to carry out operational control, detecting failures occurring at the electrodesbefore, during and after implantation (Swanson et al., 1995). Currently all cochlear implant devices include a telemetry system for checking the operation of the impedance of each electrode in the system and the electrical interaction between them (Tykocinski et al., 2005). The telemetry system allows us to test the basic functions of a cochlear implant (the communication between the external and the internal components) and to detect the electrical problems in each electrode (short circuit between electrodes, open circuits due to cable cut off) (Schulman, 1995).

The latencies of these waves are 1-2 ms shorter than the latencies of the waves obtained by acoustic stimulation due to external and middle ear by pass, and due to cochlea as well, operating directly in the cell body of spiral ganglia (Dillier et al., 2002).

An independent evaluation of the electrodes to verify the functionality of each one should be carried out in order to set up an implantable multi-channel system. An auditory detection level is estimated for each channel by electrical stimulation and also the maximum level of comfort (MLC most comfortable level) or maximum level of stimulation that the patient bears without a discomfort (Snyder et al., 2008).

I.2.1.1. Research of the ”electro-neural synapse” functionality

Introduction

The electrode impedance is a method of measuring resistance encountered by electricity passing through wires, electrodes and biological tissue (Finley et al., 2008). It is calculated as the ratio of the effective voltage applied to a particular circuit and the actual amount of electrical power intensity absorbed by the circuit. The unit of impedance is the ohm (Ohm). The electrodes impedance does not confirm the electrode placement and neither replace the radiographies after the implant (Dorman et al., 1992, Newbold et al., 2014).

Main articles published in this field:

- Oana Manolache, Raluca Olariu, Luminița Rădulescu, **Sebastian Cozma**. Electrically Impedances Variations Values In Patients With Cochlear Implant. *Romanian Journal of Oral Rehabilitation.* 2012; 4(2): 22-28.

Scientific contributions /Clinical implications:

- The study of the impedance variations in the auditory rehabilitation with cochlear implant was the first of its kind carried out in Romania, being part of a more extensive doctoral research. The comparative intraoperative and postoperative information are clinically useful for the fitting of the implant system, but also for remote diagnosis in case of technical defects of the implant.

Objectives

The aim of this study was to investigate the impedance values changes of the intracohlear electrodes implanted in patients over a period of three months, the measurements at three different times being taken as reference: during surgery, during the cochlear implant activation (1 month postoperatively) and two months after that. There were taken into

consideration the following effects on electrical impedance values: the electrode type, the topography of the electrodes, the surgery, how fast the tissue heals after surgery, changes in the intracohleare electrolyte, the lack of electrical stimulation for a period of one month after surgery.

Material and methods

There were 72 hearing loss subjects who got the cochlear implant that have been recorded on each implanted ear, electrode impedance resulting in a total of 80 "study units" (a total of 8 patients were implanted bilaterally). The criteria of choice were:

- the complete insertion of the portelectrode in the cochlea;
- the existence of intraoperative impedance measurements, when the device is activated and three months after the surgery;
- the implant was carried out with one of the following devices: Medel Pulsar CI100 and Sonata TI100 type, type Cochlear Nucleus CI22, CI24 and Nucleus Nucleus Freedom, Neurelec Digisonic type SP, SP Digisonic multiarray and SP Digisonic binaural and Advanced Bionics HiRes Focus Helix type.

After analysing the study group we noticed a relatively balanced gender distribution as follows: 49% (35) female subjects and 51% (37) male subjects. Most subjects were children (81% children and 19% adults).

The 72 subjects (80 study units), depending on the type of implanted device and taking into account the particular situation among some of them, were divided into the following seven groups:

- Group 1: 9 subjects with Nucleus 24R cochlear implant;
- Group 2: 23 subjects with Pulsar CI 100 cochlear implant;
- Group 3: 5 subjects with Sonata IT 100 cochlear implant;
- Group 4: 19 subjects with Digisonic SP cochlear implant;
- Group 5: 6 subjects with Digisonic Binaural cochlear implant;
- Group 6: 9 subjects with Advanced Bionics HR90K cochlear implant;
- Group 7: 3 subjects who had special problems, were implanted with different devices such Nucleus24R, DigisonicSP MultiArray, Advanced Bionics HR90K (Fig. I.2-1.1).

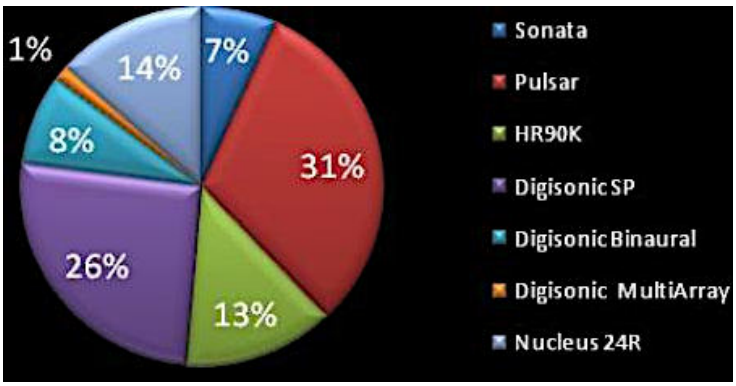


Fig. I.2-1.1. Distribution of number of subjects by category of implants

The electrodes impedance measurement. In order to perform these measurements we used a digital cochlear implant connected either directly or through the sound processor. The measurement process was controlled by a computer and the available interfaces were used as hardware interfaces available from each producer company to be connected to the cochlear implant as well as the software interfaces.

Creating the database. We created a database containing the results obtained by measuring the electrode impedance for each patient at successive moments as required in the

protocol. The results were gathered during the scheduled sessions as follows: the day of surgery, the implant activation day (one month after the implantation) and two months after the activation.

Results and discussions

The electrodes impedance recording went very well with all the patients as a routine method, and there were no problems with children cooperation, so the method is a reliable and reproducible as confirmed by several studies (Henkin et al., 2006, Hughes at al., 2001, Paasce et al., 2006, Neuburger at al., 2009). Group 1 included 9 subjects implanted with Cochlear Nucleus 24. Analysing the chart can notice a symmetric increase in the figures at 1 month after surgery, while keeping the same difference between the values measured during the first measurements on all electrodes. After two months of electrical stimulation there was a return to the previous values close to the intraoperative ones on the electrodes 3 - 22, the electrodes 1, 2 values having a slight upward trend compared to the previous determination (Figure I.2-1.2).

The second group was represented by 23 subjects implanted with the Medel Pulsar CI100 device. Figure I.2-1.3 shows an increase in impedance values postoperatively, the growth being greater in the basal electrodes (9, 10, 11, and 12). There is also a constant trend of values at approximately same level as measured 2 months postactivation compare to the activation time. Figure I.2-1.4 illustrates the results acquired on 5 subjects that are part of the 3rd group, subjects implanted with the Medel Sonata device. There is a significant increase in the average impedances values in all the apical and basal electrodes (1-4, 9-12) at one month after the surgery and a slight increase of these values in the medial group of electrodes (5-8). This increase is followed 2 months later by a slight decrease in the impedance electrode with approximately the same number of units.

The results for the fourth group, which included 19 patients implanted with Digisonic device type DigisonicSP are illustrated in Figure I.2-1.5. There is a slight upward trend of values in this group of subjects for the apical to basal electrode impedance during all three phases established by the study protocol. The trend of increasing values can be noticed when comparing the data measured intraoperatively with those at one month after surgery and compared with the data measured at the activation of the implant and after two months since the electrical stimulation.

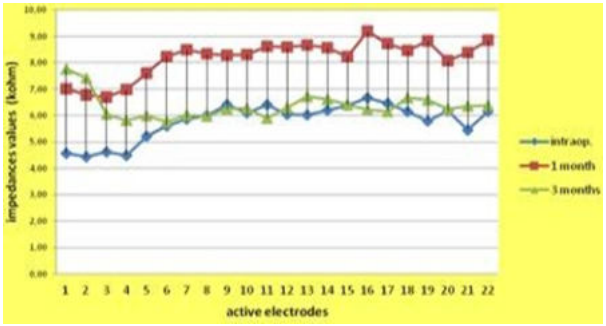


Fig. I.2-1.2. Evolution of the average values of impedances of each active electrode for Cochlear Nucleus 24

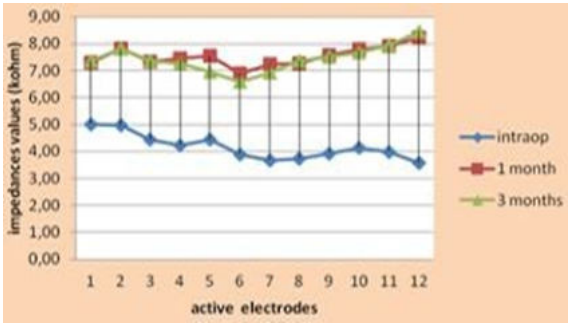


Fig. I.2-1.3. Evolution of the average values of impedances of each active electrode for Medel Pulsar

The results presented in Figure I.2-1.6. are for the 5th group, which included 5 subjects with bilateral cochlear implant carrying the Digisonic Binaural device type.

The average of impedance values for each electrode measured in all the patients in those 3 times set by the study protocol, shows a growth in values one month after the cochlear implant. There is a different variation of impedance electrodes 2 months after activation, depending on

their intracochlear location: increasing values in the basal electrodes, lowering them to the apical electrodes and maintain approximately the same value at medial electrodes.

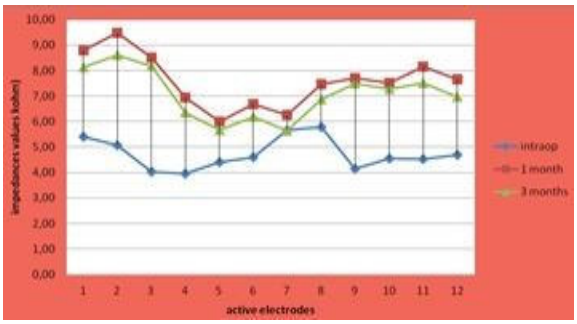


Fig. I.2-1.4. Evolution of the average values of impedances of each active electrode for MedEl Sonata

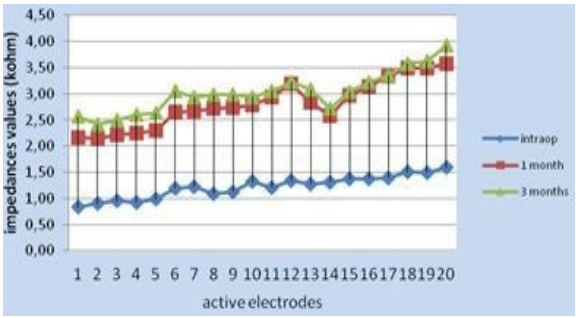


Fig. I.2-1.5. Evolution of the average values of impedances of each active electrode for Digisonic SP

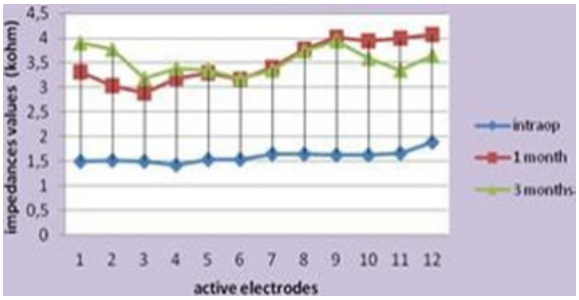


Fig. I.2-1.6. Evolution of the average values of impedances of each active electrode for Digisonic SP Binaural

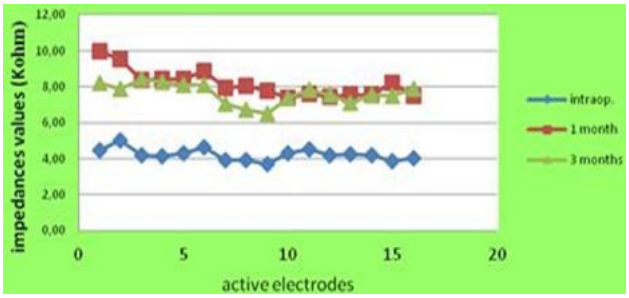


Fig. I.2-1.7. Evolution of the average values of impedances of each active electrode for Advanced Bionics HR90K

Subjects included in the 6th group, consisting of 9 subjects wearing the Advanced Bionics cochlear implant type HR90K, acquired an increase in the average electrode impedance values at activation, followed by a slight decrease 3 months after surgery **(**Fig. I.2-1.7). Two months after activation there are variations of the apical impedance electrodes and uniformity of the values for the medial and basal ones.

The last group consists of 3 subjects who were special cases. They were implanted with 3 different types of devices: Nucleus 24R, Digisonic MultiArray and Advanced Bionics HiRes90K. The first subject is a child with inner ear malformation (single cochlear cavity) and he was implanted with an Advanced Bionics device type - HiRes90K. High impedance is observed intraoperatively on 15 electrodes. These values were decreased in activation of the implant and continued their downward trend within three months after. As a special feature there can be noticed a huge difference between the intraoperative and the successive values from 25 Kohm to values around 5 Kohm (Fig. I.2-1.8).

The second subject of this group misses the 1-13 electrodes records during three months, because after the implant activation, during the adjustments after 1 month there came the need to be disconnected from electrodes 1-13 because they were creating an unpleasant and aggressive auditory sensations. Electrodes 2, 4 and 5 could not be identified intraoperatively, without impedance values recording, which can mean either a machine failure or deterioration of electrode because of insertion manoeuvres.

Unlike other patients with Nucleus enrolled in this study, at this patient, although impedance values tend to decrees from 1 month to 3 months, they remain stubbornly high to the intraoperative values (Fig. I.2-1.9.).

During the imaging examinations performed at preimplantation, one of the subjects presented the appearance of ossified cochlea, and a double electrode device was used for implantation. In this case we can notice the absence of the impedance recording for 2 electrodes of a portelectrod, and for one electrode of the second one. Probably some damage was done during the electrode insertion manoeuvres, very likely taking into account the difficulty of the case, which dealt with a bone insertion into two channels, in a completely ossified area (Fig. I.2-1.10.). Impedance values are kept largely between 1-5 Kohm, as well as for the patients with normal cochlea, although in this case the air leakage or fluid environment around the electrode is entirely absent. This case is special because the impedance increases significantly after 3 months on most electrodes.

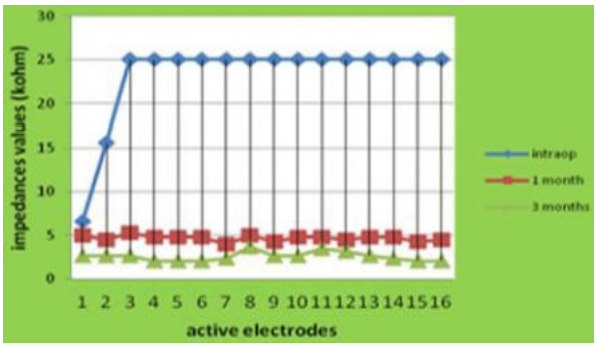


Fig. I.2-1.8. Graphical representation of electrode impedance values in a patient with a single cochlear cavity

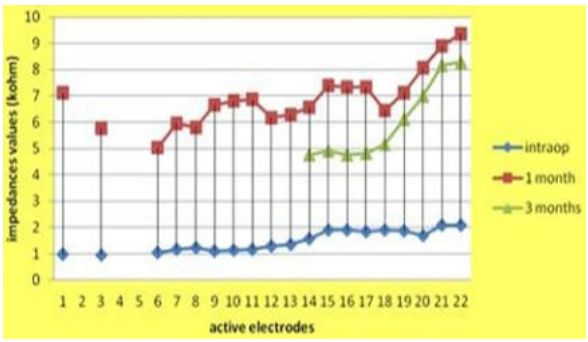


Fig. I.2-1.9. Graphical representation of electrode impedance values at the second subject

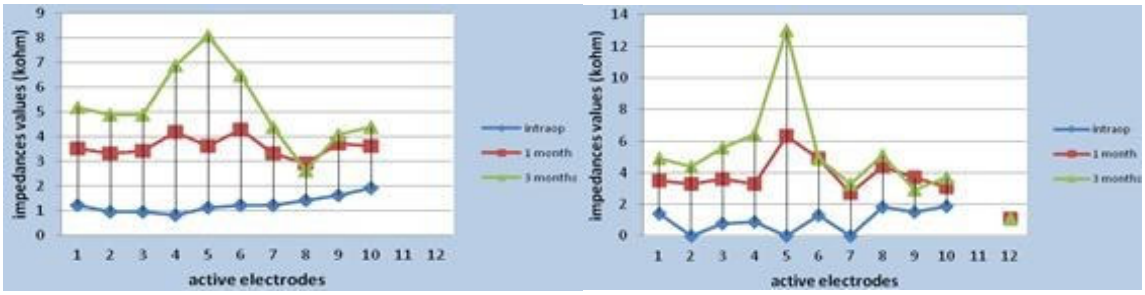


Fig. I.2-1.10. Graphical representation of electrode impedance values in a subject with ossified cochlea

Conclusions

Because of the absence of the electrical stimulation, during the time between surgery and the device activation, there is an increase of impedance on all electrodes in all models of cochlear implant. This can be explained by local postoperative tissue repair process. After studying the four brands we found out that for Nucleus implants after surgery the impedance tend to increase after 1 month then they come back around the values measured intraoperatively at a 3 months interval. For all other brands this trend of increased postoperative impedance is maintained, but even though from one month to three months there are generally decreasing values on most electrodes, they remain significantly higher than intraoperative measurements.

In terms of cochlear malformations, impedance values profile is different from the one we encounter in patients implanted with normal cochlea, this profile varies depending on the available electrode in the malformed cochlea. The intraoperative impedance values and their postoperative fluctuations are part of the common trends specific to each brand separately. Besides the parameters related to the device, the individual organic features of the inner ear may play an important role, as confirmed by the patients from the latest group of study.

I.2.1.2. The electric compound auditory potential – an indicator of electrical signal's transfer

Introduction

The electric compound action potential is a synchronous response resulting from electrical stimulation of cochlear nerve fibres and it is the electric version of the I wave of the acoustically stimulated auditory potentials of the brain stem (Snyder et al., 2008). In the same way that early auditory evoked acoustic potentials are recorded, that is those obtained by acoustic stimulation with click or tone-burst, we can get responses of the brainstem auditory nerve and electrical stimulation of the Corti ganglion using the cochlear implant. The recording of the evoked compounded action potential (ECAP) of the cochlear nerve in the case of cochlear implants constitutes an instrument of orientation for establishing the auditory threshold of detection, essential elements in the adjustments of these prosthetic devices in children (Lai, Dillier, 2007, Abbas et al., 2004). The obtained results depend on multiple factors, some connected with electro-physiological particularities of the auditory system of the patient, such as the quality of peripheral nervous fibers and their capacity of synchronization, refractory period etc., and others connected with the surgical performance (intracochlear insertion of the portelectrode and the correct choice of technological recording parameters (Alvarez et al., 2007, van Dijk et al., 2007). The MedEl implant models Pulsar CI 100 and Sonata TI 100 feature the possibility of automatic recording of ECAP with the purpose of using the results for achieving an optimal implant tuning, in children, who do not collaborate for establishing the subjective detection thresholds. The method conceived by the producer of the implant and integrated in the Maestro program of assistance was named ART - auditory response telemetry.

Main articles published in this field:

- Dan. V. Mârţu, **Sebastian Cozma**, Daniel Rusu, Aurel Curcă, Laura Ungureanu, Cristian Mârţu. Evoked compound action potential (ECAP) of the auditive nerve recorded from a group of children using Pulsar CI 100. *Timişoara Medical Journal.* 2008; 58 (3-4): 151-154. ISSN 1583-5251

Scientific contributions /Clinical implications:

- The telemetric response of the cochlear nerve measured intraoperatively and postoperatively confirms the proper functioning of the electro-neural loop and is also a diagnostic tool for the device. The electrical stimulation values at which the neural response occurs are indicative especially in the implant settings in young children. It was the first publication in Romania to evaluate the neural response in children with cochlear implants.

Aim of the study

The purpose of the study was to determine to what extent the intraoperatory recording of ART (Auditory Response Telemetry) had results. Also, we studied in our patients the relationship between ART and the etiology of deafness, its duration, auditory remainders and the position of intracochlear electrode.

Material and methods

The study included ten children with bilateral profound deafness who underwent bilateral cochlear implant, aged between two years and two months and eight years. The debut of deafness was congenital in eight cases, perilingual in one case and with ototoxic cause and postlingual in one case of meningeal deafness.

The etiology of deafness in the other eight children with congenital debut was: hereditary in three cases, heredity and perinatal factors (prematurity, hypoxia at birth) in one case, and undeterminated for the others. We established a protocol of electro-physiological evaluation of the 10 children implanted with MedEl system, type Pulsar CI 100. After completion of the surgical intervention, under general anesthesia we performed the impedances mesurements. We recorded the amplitude growth function through the Maestro Software version 2.0.1, the recorded electrode being close to the stimulated electrode. (Fig. I.2-1.11)

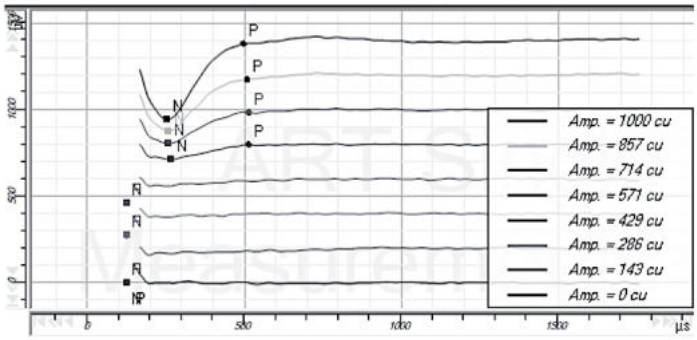


Fig. I.2-1.11. ECAP measurement results (auditory response telemetry ART)

The stimulation parameters of the electrodes were the following: the duration of phase 30µs, minimum amplitude 0 current unities, and the maximum amplitude was variable, depending on the response, maximum 1000 units. In addition, the optimal measuring delay interval (recording delay) was searched individually. The interpretation of the results consisted in the visual identification of the reproducible positive and negative peaks of ECAP, the detection of the threshold being considered the lowest value of intensity in which these appear.

After the intraoperatory recording of ECAP under general anesthesia, in every case we have verified radiologically the cochlear position of the portelectrode.

Results and discussions

In six patients a complete insertion of the 12- channel electrodes was realized, and were evident on the radiographs: in one patient - one extra-cochlear electrode, in two patients - two extra-cochlear electrodes per patient, and three extra-cochlear electrodes in another case.

The impedances were normal for all patients in all the 12 channels of every implant.

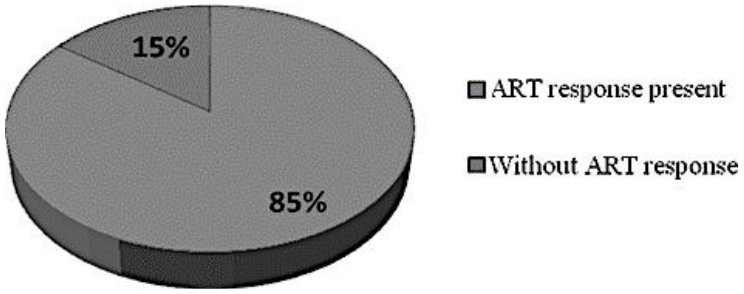


Fig. I.2-1.12. The percentage of the electrodes on which the ECAP responses were obtained.

We performed in every patient the maximum of admitted recordings by the particular situation of every intervention. All electrodes were tested in three patients, and in certain situations we tested at least four electrodes situated equidistantly on the port-electrode. We tested in total 70% from the implanted electrodes, and the testing ended with the collecting of ECAP in 85% from the measured electrodes (Fig. I.2-1.12).

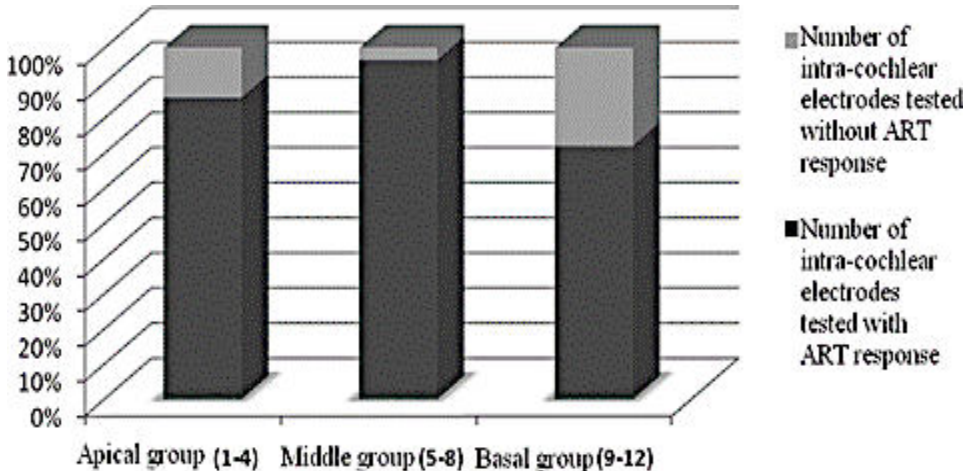


Fig. I.2-1.13. Representation of ART obtaining on groups of electrodes (basal, medial and apical).

ART could be recorded in good conditions in the majority of the patients on the intra-cochlear electrodes.

The quality of the response varied, depending on the position of the portelectrode in the cohlea. We obtained better responses of the auditory nerve for the electrodes situated in the medial cochlear portion and less ample for the basal portion (Fig. I.2-1.13). Determined auditory thresholds were higher for the group of basal electrodes than those from the medial or apical cochlear region.

We could not establish a dependence of ART on the duration of auditory privation, but a more deteriorated ART response was observed in the hypoacusia of meningeal cause.

We could not demonstrate, in our group of patients, the observations of other published studies according to which ECAP is better collected if there were auditory remains on the implanted ear than in the case of complete auditory deprivation (Basta et al., 2007). The percentage of ART obtained is even better for the patients without auditory remains (86% compared to 77%).

Conclusions

We obtained ART responses in an important proportion, on 85% from the tested intra-cochlear implants. In the case of profound insertion, the ART response is better in all the tested electrodes. The most degraded ART response was recorded in the child with sensori-neural hearing loss, where we collected a response only from two of the four measured channels.

ART was better collected in the middle portion of the cochlea and worse in the basal portion. We could not establish a relationship between the age of implantation and the quality of ART response, and ART responses in children with auditory remains on the implanted ear were not better.

The ART proved to be an important instrument, which could be used with the aim to adjust the cochlear implants in child, except from those with deafness of meningeal cause. ART is a good indicator of the intra- and extra-cochlear electrodes.

Other articles published in this field:

- Oana Bitere, **S. Cozma**, C. Mârțu, Dan Mârțu, Raluca Olaru, Luminița Rădulescu. Evoked compound action potential of cochlear nerve in the evaluation of electroneural loop in patients with cochlear implant. *The Medical-Surgical Journal. 2016;* 2 (s. 1): 43-54. ISSN: 0048 - 7848

I.2.2. Research regarding the auditory neural plasticity: the effects of the electrical stimulation on the maturation of the auditory brainstem pathways

Background

Multiple-channel cochlear implants overcome basilar membrane or cochlear hair-cell damage by encoding acoustic information and providing electrical stimulation directly to the auditory nerve. Spectral information is transmitted to the auditory nerve by allocating a frequency range to each stimulation-electrode channel according to the cochlea's tonotopic organization. As a result, high- and low-frequency sounds are conveyed by electrode channels located at, respectively, the basal and apical ends of the cochlear implant electrode array. The stimulation delivered to the auditory nerve is then conveyed through the brainstem auditory pathways much as in acoustic processing in normal-hearing subjects. It is of neurophysiological interest to determine how auditory brainstem developmental plasticity can be promoted by chronic electrical stimulation in children who have never heard before.

Previous studies have suggested that ABRs continue to follow maturational processes after birth (Hecox, Galambos, 1974, Teas et al., 1982, Krumholz et al., 1985). Specifically, ABR wave I, III and V latencies have been shown to decrease with conceptional age (i.e., age at time of birth plus days of life) (Starr et al, 1977). Accordingly, normative data have been developed for ABR latency as a function of conceptional age, providing indirect markers of auditory nerve and brainstem pathway maturation. For full-term infants, the chronology described by Uziel et al. (1980) suggests that adult latency values will be reached by 2–3 months post-birth for ABR wave I (auditory nerve), by 8–12 months for wave III (lower brainstem) and by 12–24 months for wave V (upper brainstem). This pattern of ABR maturation in hearing children over their first two years of extra-uterine life is now well established. When reanalyzing ABR latency data from the literature, Eggermont (1985a) found that a model utilizing two exponential decay functions provided the best fit (i.e., minimum mean square error) with respect to the ABR maturational time-course. Wave V latency maturation, up to 100 weeks' conceptional age (see Fig. I.2-2.1), could be well fitted by the sum of 2 decaying functions, with time-constants of 4 and 50 weeks (Eggermont, 1985a).

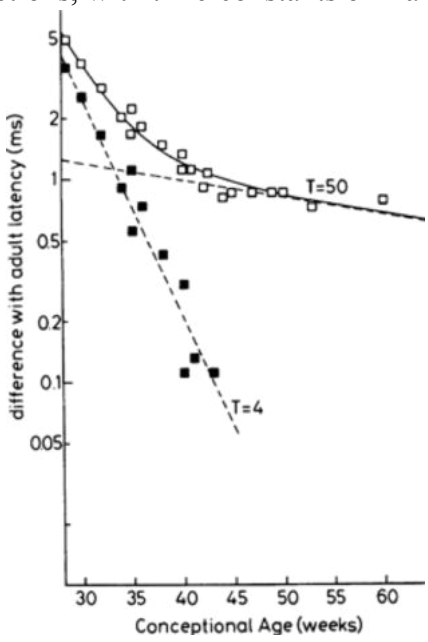


Fig. I.2-2.1. Modeling of ABR wave V maturation in normal-hearing full-term infants (adapted from Eggermont, 1985a). Data from different institutions were analyzed. To make sure that the observed changes in latency were due to a maturational effect and not biased by any across-institution differences in ABR recording equipment, differences with respect to adult wave V latency (as measured in the same clinic and with the same equipment) are plotted as a function of conceptional age. The maturational time course of wave V latency is well fitted by the sum of two exponential functions with time constants of 4 and 50 weeks respectively. Solid symbols correspond to the early portion of the curve after correction for the contribution of the second exponential function.

This model was sufficiently robust to accurately account for ABR data from various institutions, providing a valid tool for predicting normal ABR latency maturation. Interestingly,

the first, most rapidly decaying exponential function was found to fit the early rapid maturation of wave I (the compound action potential of the auditory nerve) for which latency reaches adult values at 45 weeks – i.e. slightly after term birth (Eggermont, 1992). The second decaying exponential function, with a slower time-constant, might be interpreted as reflecting the maturation of auditory brainstem structures.

Arguments in favor of activity-dependent central auditory system plasticity were reported for deaf children receiving cochlear implants. Ponton et al. (Ponton et al., 1996b, Ponton, Eggermont, 2001) compared the maturation of cortical auditory evoked potentials (in particular, the P1 response – also known as P50, and thought to originate in the primary auditory cortex) in age-matched normal-hearing and cochlear implant children in response to acoustic clicks and biphasic current pulses, respectively. The chronological pattern of maturation was approximately the same in the cochlear implant group, but with a delay matching the period of auditory deprivation (Ponton et al., 1996a). Taken together, the above data on sensory deprivation period, age at implantation and time of onset of deafness highlight the role of the time in sound (pre- and post-implantation) as a critical factor for investigating auditory pathways maturation in cochlear implant recipients.

Main articles published in this field:

- Hung Thai Van, **Sebastian Cozma**, Florent Boutitie, François Disant, Eric Truy, Lionel Collet. The pattern of auditory brainstem response wave V maturation in cochlear implanted children. *Clinical Neurophysiology.* 2007; 118: 676–689, (IF=2,468).

Scientific contributions /Clinical implications:

- During my stage in Lyon, France, I participate to a study finalised with the publication of one of the first articles in the world showing the maturation of the auditory neural pathways under electric stimulation offered by the cochlear implant. This was a very important finding, the neural transmission speed depending on the electrical stimulation and conditioned by the onset of deafness and the etiology.

Introduction

Beyond the well-documented maturation of cortical auditory evoked potentials, only a few studies have pointed out that EABR latencies may likewise change over time after implantation. Repeated measurement of EABR wave latencies in cochlear implant children with congenital deafness has nevertheless led to the conclusion that brainstem auditory pathway conduction velocity can significantly decrease over the period between initial stimulation and at least 1-year's implant use (Gordon et al., 2003, 2006). To our knowledge, potential changes in EABR latencies after implantation have yet to be investigated beyond 1 year of implant use. In addition, very little is known about EABR maturation in children with later onset of deafness.

This distinction is important because those children, as opposed to congenital deaf children, did have some auditory experience before the auditory rehabilitation. The EABR waveform pattern is similar to that of ABRs – but without wave I, which is masked by the electrical stimulus artifact – although the EABR usually appears 1.5–2 ms earlier due to the direct stimulation of spiral ganglion cells by the implant electrodes (Starr Brackmann, 1979). By analogy with the normal ABR, EABR wave III is thought to be generated in the midbrainstem and EABR wave V in the upper brainstem (van den Honert, Stypulkowski, 1986).

Aim of the research

Central to this study is the comparison between maturation of electrically evoked auditory brainstem response (EABR) in implanted children and acoustically evoked brainstem responses (ABR) maturation in hearing children. We focused on wave V since it is the most robust EABR component obtained on more implant electrodes and for more stimulus intensities than the others (Firszt et al., 2002). Following Eggermont (1988), wave V latency was used as the variable of interest to assess auditory brainstem response maturation in young cochlear implant recipients. We sought to answer the following questions: (1) Does the evolution of EABR wave V latency over the first 2 years of cochlear implant use follow a pattern similar to that seen in ABR of hearing children in the first 2 years of life? (2) To what extent can the time of onset of deafness affect wave V maturation? In order to address these issues, changes in EABR wave V latency were analyzed for the 2-year period following cochlear implant connection in two distinct groups. The first group consisted of children with early-onset deafness (congenital for most of them) and the second of children with late-onset deafness. Exponential decay models, adapted from the model of Eggermont, were tested in both populations to fit the changes in wave V latency over a two- year period from the time of implant connection. It was hypothesized that auditory maturational processes were likely to have begun before implantation in children with late-onset deafness, but to have started only after cochlear implant connection in the congenitally deaf children. By analogy with the biologically realistic model of ABR maturation described by Eggermont (Eggermont, 1985a), we further predicted that maturation of wave V latency in children with early-onset deafness would be fit by the sum of two decaying exponential functions, one reflecting maturational process at the most peripheral level and the other at the level of the brainstem. Our underlying assumption was that the chronological pattern of wave V maturation in this group would resemble that described in normal-hearing children, as it is the case for cortical auditory evoked potentials.

Subjects and methods

Subjects. A total of 55 children (24 girls, 31 boys) participated in the study. All met the following inclusion criteria: children with profound deafness; receivers of the Nucleus® 24 multichannel cochlear implant (CI24M system), with full insertion of the stimulation electrodes (standard straight electrode array).

There was an important difference between two sub-groups of the children regarding the onset of profound deafness. One subgroup consisted of 41 children who had either been born deaf or had developed deafness during the first months of life:

• thirty-six of these children were congenitally deaf: cause of deafness was genetic in 16 cases, of infectious origin in 4 (cytomegalovirus disease: 1 case; rubella: 3 cases), neonatal anoxia in 2, unknown in 14;

• three subjects were not diagnosed as deaf at birth but had developed delayed profound deafness diagnosed around 6 months of age;

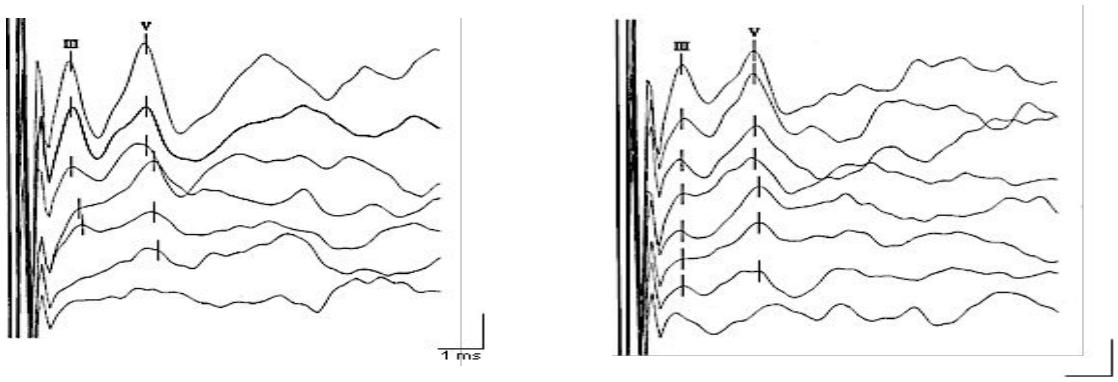
• two became deaf during the first months of life following meningitis: both were diagnosed as profoundly deaf (bilateral absence of ABR to 100-dB acoustic stimuli) at the age of 7 months.

These children had undergone cochlear implantation at between 1 year 2 months and 12 years 5 months of age (mean = 3 years 4 months). In addition to this early-onset deafness group, a second subgroup comprised 14 children who had developed deafness after the first year of life. The subjects in this second subgroup ranged in age from 1 year 2 months to 4 years 2 months at the time of onset of deafness with a mean age of 2 years 1 month. Cause of deafness was meningitis in five of these children (mean age at deafness onset = 1 year 11 months), familial in four (mean age at deafness onset = 2 years 1 month), and unknown in five (mean age at deafness onset = 2 years 3 months). In this second subgroup, age at implantation ranged from 2 years to 17 years 4 months (mean = 7 years 4 months).

All the children in this study had worn a conventional hearing aid before undergoing CI. The period of auditory deprivation was estimated as the interval between the onset of deafness and the time at which the child first used conventional amplification: a mean of 1 year 1 month in the early-onset deafness group and a men of 7 months in the late-onset group.

EABR recordings. EABR data were gathered at the end of the regular cochlear implant fitting sessions. Electrical stimuli were generated using the manufacturer's interface device (Dual Processor Interface, Cochlear Corporation, Basel, Switzerland) connected to a computer via a serial port. This system also triggered the evoked-potential measurement device (CA 2000 system, Nicolet Biomedical). EABRs were tested for two stimulation electrodes: one located at the basal end of the implant electrode array (electrode 5), and the other at the apical end (electrode 20). EABRs were measured in response to monopolar stimulation (biphasic pulse trains of duration = 25 s/phase) delivered at a rate of 11.4 Hz. The programming set-up used arbitrary units ranging from 1 to 255 Cochlear Corporation programming units (p.u.) (increasing by steps of ~2% per unit) – i.e., a non-linear progression from ~10 to 1.750 μA. Responses were filtered with a 150–1500 Hz analog band-pass filter and amplifier sensitivity was set at 100 μV. An analysis time of 10 ms was used, with a sampling rate of 25 kHz. For each EABR trace, the averaging process involved 1000 sweeps.

Wave V latency measurement. To verify the reproducibility of the EABR peaks obtained, two averages of 1000 sweeps were collected at that level, which usually ranged between 190 and 200 p.u. (i.e., between 469 and 574 μA). The experimenter then decreased the stimulus level by 5 p.u. steps down to the extinction of wave V, which defined the EABR threshold (Fig. I.2-2.2.). In agreement with literature data, including previous work by our own team, wave V latency was found to be insensitive to stimulus intensity at high intensities (Gordon et al., 2003, van den Honert, Stypulkowski, 1986, Gallego et al., 1999), but to increase with decreasing stimulus intensity over the lower half of the cochlear implant's electrical stimulation range, with a noticeable latency increase at the level of the EABR threshold (Firszt et al., 2002, Gallego et al., 1996, Shallop et al., 1990).



a. b.

Fig. I.2-2.2. EABR recordings obtained with decreasing stimulation levels in a 3-year-old girl after 1 year of implant use. (a) EABR recordings at the basal end of the cochlear implant electrode array (electrode 5). (b) EABR recordings at the apical end of the electrode array (electrode 20).

Data analysis. We analyzed changes in EABR wave V latency over the 2 years following cochlear implant connection, in the early- and late-onset of deafness groups. In the early-onset of deafness group, the follow-up started, at the latest, 2 months after CI connection. In the late-onset deafness group, the follow-up started at the latest 1 week after connection for all subjects.

Each individual series of measurements included data from 5 or more of the following test times: day of cochlear implant connection, 1 week post-connection, and 1, 3, 6, 9, 12, 18

and 24 months post-connection. Accordingly, individual changes in wave V latency as a function of post-connection time were analyzed in all 55 children for electrode 20 and in 42 children for electrode 5. The potential interactions of these effects with the rate of latency change were also tested. Following Eggermont (Eggermont, 1985a), biologically realistic fitting models using decaying exponential functions were then tested on the basis of the best fit with respect to minimum mean square error. Statistical analyses were performed with the SAS 8.0 software package (SAS Institute, SAS Campus Drive, Cary, NC). The parameters of the most appropriate decaying exponential model were estimated with SAS's ''Proc Mixed'' and ''Proc Nlin'' procedures.

Results

Individual changes in EABR wave V latency after cochlear implant connection.

A total of 668 EABR wave V latency values were measured in children with early-onset deafness versus 168 in the late-onset group. There was no significant difference in the number of observations between children with early- and late-onset deafness for electrode 5 (heteroscedastic t-test: $t(17) = 0.45$, $p = 0.66$) or electrode 20 (heteroscedastic t-test: $t(24) = 0.34$, $p = 0.74$). On average, wave V latency was found to decrease over time in children with early-onset of deafness for both electrodes 5 and 20, with respective mean starting values of 4.23 and 4.12 ms and mean final values of 3.63 and 3.48 ms. For the same observation period, a very slight decrease in mean latency values was seen in children with late-onset deafness (electrode 5: from 3.99 to 3.82 ms; electrode 20: from 3.83 to 3.65 ms).

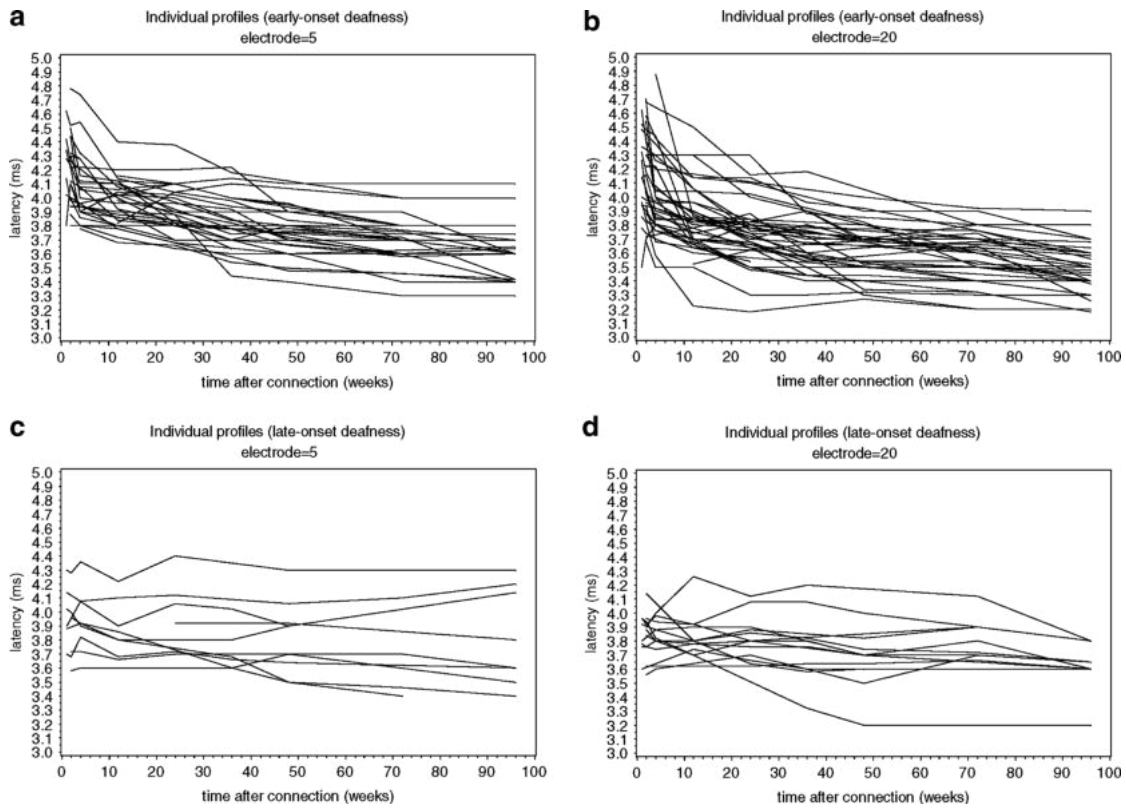


Fig. I.2-2.3. Individual patterns of decrease in wave V latency for the two test groups. Individual changes in wave V latency are shown for electrodes 5 and 20 in children with early-onset deafness (diagrams 3a and 3b), and with late-onset deafness (diagrams 3c and 3d).

Fig. I.2-2.3. shows individual patterns of wave V latency decrease for the two test groups. Although there was considerable heterogeneity in response level across subjects, a general

pattern of EABR wave V maturation emerged in children with early-onset of deafness. These children exhibited a rapid decrease in wave V latency during the first 10 weeks of implant use, followed by a slower decrease. Conversely, in all but two subjects with late-onset of deafness, no decrease in wave V latency was observed, irrespective of test electrode.

Fitting models using decaying exponential functions. As well as log-transforming the original data to build a linear model, it was also possible to fit the original data with a decaying exponential model, adapted from the Malthus model of exponential growth. The changes in wave V latency could be modeled as the sum of two decaying exponential functions with respective time-constants of 3.9 weeks (T0) and 68 weeks (T1). The model thus allowed for the initial rapid decrease in latency values followed by a slower decrease.

The final latency values, as predicted by the double exponential model, are shown in Table I.2-2.A. Comparison of goodness-of-fit between the simple exponential model and the double exponential model confirmed that the double exponential model provided a better fit (F statistics based on residual sums of squares, $p = 0.03$).

Early-onset deafness				Late-onset deafness			
Electrode 5		Electrode 20		Electrode 5		Electrode 20	
Average	95% confidence interval	Average	95% confidence interval	Average	95% confidence interval	Average	95% con
3.62	3.57–3.68	3.50	3.45–3.55	3.79	3.70–3.87	3.67	3.58–3.7

Table I.2-2.A. Wave V latency values (ms) at 96 weeks post-connection, as estimated by the decaying exponential model, according to subjects group (early- or late-onset of deafness) and test electrode

Discussion

Conditions and time-course of auditory brainstem maturation in children receiving a cochlear implant. Using repeated electrophysiological measurements in cochlear implant children with early-onset of deafness, Gordon et al. (Gordon et al., 2003, 2006) were the first to demonstrate a shortening of EABR wave III and V latencies and a decrease in neural conduction times in the lower and upper brainstem throughout the first year of implant use. Here we focused on modeling changes in EABR wave V latency (i.e., neural conduction in the upper brainstem) occurring during the initial 2 years of implant use. The 2-year evaluation is necessary for a more complete comparison with hearing children where ABR maturation typically ends at roughly 2 years of age (Eggermont, 1992; Eggermont, Ponton, 2003; Fria, Doyle, 1984). The wave V latency values predicted by our modeling at 2 years were shorter than those predicted by Gordon et al. (2002, 2003, 2006) for children with 1 year of implant use (>4 ms at basal electrode 3) though in line with the values reported in adults by our group (Gallego et al., 1996, 1997, 1998) and by other researchers (e.g., 3.69 ± 0.14 ms at the apical end of the array and 3.76 ± 0.20 ms at the basal end (Firszt et al., 2002)). It is possible that the decrease in EABR wave V latency may reflect not only maturation of the upper auditory brainstem per se, but also maturational changes affecting the lower auditory brainstem (EABR wave III) or even the responses of the auditory nerve to electrical stimulation (i.e., the electrical compound action potential (ECAP N1 wave) and EABR wave II). However, our model of EABR wave V latency changes is in line with previous research on EABR including an analysis of peripheral components and interwave latency changes. Analyzing EABR measurements taken at 0, 2, 6 and 12 months after connection, Gordon et al. (Gordon et al., 2006) found wave V latency decreases at all test sessions.

Comparison of developmental plasticity of the auditory brainstem in normal-hearing children and children with cochlear implants. Eggermont (Eggermont, 1988) showed that the maturation of sensory evoked-potential latencies can be well fitted using the sum of decaying exponential functions, irrespective of sensory modality (auditory,

somatosensory or visual). In all examined cases, decreases in latency could indeed be described as a combination of fast and slow processes with respective time-constants around 4 and 50 weeks (Eggermont, Salamy, 1988a). For acoustically evoked ABRs in normal-hearing children, the short time-constant process is completed shortly after birth (from 40 to 45 weeks' conceptional age), while the slower time-constant process reaches adult latency values by 3 years' conceptional age (Eggermont, 1992). Eggermont (1985a) interpreted the first rapid time-constant as reflecting the maturation of ABR wave I, in agreement with the notion that auditory pathway maturation follows a centripetal pattern from the auditory nerve towards central auditory neurons. The starting wave V latency was significantly longer for electrode 5 than for electrode 20 in all children, suggesting that the chronology of maturation was not the same between basal and apical electrodes. This is in agreement with previous results from our team, pointing out the immaturity of the basal part of the human cochlea in preterm neonates (Collet et al., 1987, Soares et al., 1988). It is commonly held that the spatial encoding of frequency along the human cochlea matures during development, with low-pitched sounds being represented first (Rubel, Ryals, 1983). In children with late-onset deafness, some intra-cochlear maturational processes may occur prior to the onset of deafness, leading to a tonotopic organization of the cochlea similar to that found in hearing children of the same age; that longer latency values are predicted for the basal electrode at the end of the study period is consistent with previous reports of a gradual EABR latency decrease from base to apex in adult cochlear implant recipients (Firszt et al., 2002, Gallego et al., 1996, Miller et al., 1993, Shallop et al., 1990).

Influence of onset of deafness, age at implantation and sensory deprivation period on auditory brainstem plasticity: potential clinical implications. An important issue is that of the relation between auditory pathway maturation in young cochlear implantees and their pre- and post-implantation time in sound. It is commonly accepted that age at onset of deafness, age at implantation, and duration of auditory deprivation affect to a great extent the auditory performance after cochlear implantation, as opposed to etiology of deafness (National Institutes of Health Consensus Statement, 1995). While the congenital or meningitic origin of the deafness does not seem to have much influence on post-implantation auditory performance, children who have the chance to develop an auditory memory before the implantation tend to demonstrate better performance than those who are born profoundly deaf (Gantz et al., 1994).

In the present study, neither age at implantation nor duration of auditory deprivation was found to influence changes of EABR wave V latency over the 2-year follow-up. As opposed to cortical auditory evoked potentials and middle latency auditory response maturation (Ponton et al., 1996b, Sharma et al., 2002a, 2005; Gordon et al., 2005), EABR maturation is thought to be insensitive to age at implantation. It has been reported that the age at which a child receives the cochlear implant influences neither initial EABR latency and amplitude values nor how they change over time with implant use (Gordon et al., 2003). Our results are in line with those of Gordon et al. (Gordon et al., 2006). Here we also found that age at implantation did not influence the rate of wave V latency change, thus was not a limiting factor for auditory brainstem responses plasticity. The fact that there was no influence of the duration of auditory deprivation was more surprising given the results we previously obtained in implanted patients with asymmetric duration of deafness (Thai-Van et al., 2002).

The critical role played by the onset of deafness in the present study merits discussion. Although all children in the present study were diagnosed with prelingual deafness (defined as occurring before 5 years of age), the onset of deafness clearly differed between the two tested groups. One may argue that children in the late-onset deafness group (mean age at onset of deafness = 2 years 1 month) might have a developing/mature auditory system at the time they became deaf. Moore and colleagues (Moore et al., 2002) have shown that chronic intra-cochlear electrical stimulation in adult deafened cats can induce tonotopic reorganization at the level of

the inferior colliculus. Ponton et al. (1999) developed a theory for the activity-dependent maturation of the auditory system after long periods of deafness. They proposed that the auditory pathways remain minimally plastic during the period of sensory deprivation, until auditory input provided by the implant restores the normal chronology of maturational processes. Our results in the early-onset deafness group are in total agreement with this theory.

Mechanisms possibly involved in auditory brainstem plasticity in children receiving a cochlear implant. The potential mechanisms underlying EABR maturation in children with cochlear implants can be discussed with regard to those presumably involved in ABR maturation. Well-formed myelin sheaths are observed surrounding the proximal end of the auditory nerve as early as the 26th gestational week – a time at which ABRs can be first recorded (Moore, Linthicum, 2001). At the end of gestation, myelin of mature appearance is normally visible along the auditory nerve central to the glial junction, trapezoid body, lateral lemniscus and inferior colliculus (Gilles et al., 1976). The myelination process is not, however, completed before 1 year of postnatal age in normal-hearing children (Moore et al., 1995). Importantly, the myelination of the auditory brainstem is thought to proceed in parallel with the ABR latency decrease observed during the infantile period (Inagaki et al., 1987). Since both myelination and changes in synaptic density follow a two-step process, both might explain ABR maturation as modeled by Eggermont (1985a). Ponton et al. (1996c) have made a distinction between the maturation of the different segments of the brainstem auditory pathway corresponding to whether these segments represent asynaptic (intervals I–II and III–IV) or mono-synaptic (intervals II–III and IV–V) pathway. In hearing children, the fact that the interval III–IV, assumed to reflect only axonal conduction, remains constant after birth suggests that increasing conduction velocity due to myelination totally compensates for increasing brainstem auditory pathway length from birth until age 1 (Moore et al., 1995) and possibly age 3 (Moore et al., 1996). In children with early-onset deafness, the ‘‘frozen’’ state is immature and stimulation with the implant will first cause the very early stages of maturational processes (including the initial phase of rapid synaptogenesis and myelination) to resume. The same physiological processes as in hearing children may then occur, though delayed by the period of sensory deprivation. In children with late-onset of deafness, these physiological processes may, at least in part, have taken place before the onset of profound deafness. Although plastic changes, such as increased synchrony across auditory nerve fibers, cannot be excluded (Gordon et al., 2003, Thai-Van et al., 2004), the net effect of implant use in terms of improved neural conduction time would tend to be much less marked than in congenitally deaf children. Aparently, only children with early auditory deprivation are liable to undergo significant processes of myelination and/or synaptic changes after cochlear implantation.

Conclusions

We proposed a statistical model that allows, on the one hand, the prediction of EABR wave V latency changes over the 2 years post-implant connection and, on the other hand, a comparison between children with late- and early-onset of deafness. In the latter, maturation of EABR wave V latency was found to follow the same chronological pattern as that described for ABR wave V in normal-hearing children. The findings agree with the theory of centripetal maturation from the auditory nerve towards central auditory neurons. Further, observed differences between electrode 5 and electrode 20 recordings are consistent with the notion that sound processing takes longer to mature for high-than for low-pitched sound. In addition to providing decisive arguments in favor of rehabilitation-induced plasticity in cochlear-implanted children, the present study indicates that the effect of resuming auditory input may differ greatly depending on the condition of the auditory pathways at the time of deafness onset. Further research is required to assess whether the differences we observed in terms of auditory pathway maturation are associated with consistent differences in terms of language development.

I.2.3. The state of the art in Cochlear Implant Programming – the base of global consensus

Background

Multichannel intracochlear implants have been clinically available for more than 25 years. The fitting of the processors to the individual recipient is considered to be crucial in obtaining good results. To date there is neither well described and commonly adopted Good Clinical Practice (GCP) for this act nor evidence based material to distinguish efficient procedures from less efficient ones. Over these 25 years, fitting a CI has been carried out by competent clinicians who have established their own heuristics, good practices, and empirical knowledge. It seems reasonable to believe that a critical analysis of the cumulative knowledge acquired over the years may serve as a first step towards a definition of GCP.

Cochlear implants (CI) processors must be appropriately programmed and customized for the recipient (Cope, Totten, 2003, Shapiro, Bradham, 2012). The aim of this is to set a number of parameters to ensure that the electrical pattern generated by the device in response to sound yields optimal speech intelligibility. Several electrical parameters are available and all their values together is commonly called the MAP. Finding and programming the optimal values for a recipient is commonly called the act of fitting. It is achieved using proprietary software and a hardware interface connected to the processor and depends on behavioral responses from the CI recipient.

After the initial switch-on or activation of the processor, several fitting sessions are normally required (Walravens et al., 2006). Most of the MAP adjustments take place over these first few months, until levels remain relatively stable (Walravens et al., 2006, Henkin et al., 2003). Following stabilization of electrical dynamic range, fitting sessions are usually limited to periodical checks, typically annually, as long as progress remains satisfactory. Most implant teams have an expert opinion of what the expected level of performance for an individual recipient should be and more detailed adjustments are made to the MAP if this target is not reached.

Main articles published in this field:

- Bart Vaerenberg, Cas Smits, Geert De Ceulaer, Elie Zir, Sally Harman, N. Jaspers, Y. Tam, Margaret Dillon, Thomas Wesarg, D. Martin-Bonniot, L. Gärtner, **Sebastian Cozma**, Julie Kosaner, Sandra Prentiss, P. Sasidharan, Jeroen J. Briaire, Jane Bradley, J. Debruyne, R. Hollow, Rajesh Patadia, Lucas Mens, K. Veekmans, R. Greisiger, E. Harboun-Cohen, Stéphanie Borel, Dayse Tavora-Vieira, Patrizia Mancini, Helen Cullington, Amy Han-Chi Ng, Adam Walkowiak, William H. Shapiro, and Paul J. Govaerts. Cochlear Implant Programming: A Global Survey on the State of the Art. *The Scientific World Journal.* 2014; 501738 (IF=1,219)

Scientific contributions /Clinical implications:

- This article was the basis for the elaboration of a global consensus on the programming of cochlear implants, summarizing the results of a meeting that took place in Antwerp (Belgium) in 2012. The meeting, which I had the honor to attend, was organized by EarGroup under the leadership of Prof. Paul Govaerts, and its conclusions were obtained on the basis of individual votes of representative specialists from around the world in response to the many problems related to the programming of cochlear implants in all technologies.

Introduction

The programming of CIs is essential for good performance. However, no Good Clinical Practice guidelines exist. Data indicate that general practice starts with a single switch-on session, followed by three monthly sessions, three quarterly sessions, and then annual sessions, all containing one hour of programming and testing. The main focus lies on setting maximum and, to a lesser extent, minimum current levels per electrode. These levels are often determined on a few electrodes and then extrapolated. They are mainly based on subjective loudness perception by the CI user and, to a lesser extent, on pure tone and speech audiometry. Objective measures play a small role as indication of the global MAP profile. Other MAP parameters are rarely modified. Measurable targets are only defined for pure tone audiometry. Huge variation exists between centers on all aspects of the fitting practice.

Aim of the research

This paper attempts to describe the current state of the art by providing a comprehensive inventory of the fitting strategies in a substantial number of CI centers worldwide. It is beyond the scope of this paper to explain the meaning of all possible MAP parameters or settings. For this information, the reader is referred to the companies' user manuals and to existing comprehensive overviews (Shapiro, Bradham, 2012, Wolfe, Schafer, 2010).

Material and Methods

In preparation for an international debate which was organized in Antwerp, Belgium, in October 2012, a questionnaire was distributed to 47 CI centers worldwide. All questionnaires were returned. All responses were analyzed and the data were discussed during the two-day debate. After this debate all centers were invited to a remote interview (telephone or Skype) to clarify and correct the answers where needed. In addition, the participating centers were invited to log one single fitting session in 5 consecutive recipients of one same CI brand in the months of September-October 2012. This yielded a prospective cross-sectional snapshot of the fitting procedure which served as verification for the questionnaire statistics.

The questionnaire is available online at http://dx.doi.org/10.1155/2014/501738). Briefly the questions focused on the following topics:

(i) number of implant recipients being followed and the annual increase,

(ii) brands of implants being implanted and fitted,

(iii) MAP parameters being modified from default at switch-on and during the followup,

(iv) assessments undertaken (subjective, objective, and psychoacoustic) and used to steer the MAP modifications,

(v) well defined targets used.

Descriptive statistics were used and the results are presented graphically by means of histograms or box and whisker plots. Distributions are described by medians, quartile ranges (QR: between 25th and 75th percentile), extremes (minimum and maximum), and outliers.

The term Cochlear is used for the Nucleus device (Cochlear Corporation, Sydney Australia), Med-El for the Med-El device (Med-El, Innsbruck Austria), AB for the Advanced Bionics device (Advanced Bionics Corporation, Valencia, California), and Neurelec for the Digisonic device (Neurelec, Vallauris, France). Throughout the text, the term minimum level is used for the T, THR, T, or MIN parameters of Cochlear, Med-El, AB, and Neurelec, respectively. The term maximum level is used for the C, MCL, M, or MAX parameters. In this paper the term eCAP (electrically evoked compound action potential) is interchangeable with eCAP threshold measurements and refers to (t)NRT, (t)ART, and (t)NRI for Cochlear, Med-El, and AB, respectively.

Results

Participating Centers. Forty-seven centers from 17 different countries (Australia, Belgium, Canada, France, Germany, India, Italy, Lebanon, Morocco, Norway, Poland, Romania, Spain, The Netherlands, Turkey, United Kingdom, and USA) and 5 different

continents (Europe with 60% of centers, North-America 11%, Asia 4%, Australia 4%, and Africa 2%) filled out the paper survey. All together they were following 47600 CI users with an annual increase of 4800. Twenty-nine centers had a representative being interviewed. They were following 37000 CI recipients with an annual increase of 3700. This means that the responses of 62% of the participating centers were double-checked covering 78% of the CI recipients being followed. The cross-sectional snapshot yielded data from 255 fitting sessions of 34 centers. The participating centers have an average experience of 21 years (median startup in 1991; QR: 1987–2000) and a median number of 625 implants (QR: 338–1300) with 62 new implants last year (QR 50–123).

On average each center provides three CI brands (Cochlear, Med-El, and AB); 10.5% provide only 1 brand; 10.5% provide 2 brands; 55% provide 3 brands, and 24% provide 4 brands. For all three major brands we received responses from at least 26 centers of which at least 15 were interviewed afterwards. Only Neurelec was underrepresented, with 4 centers responding on paper of which 3 were interviewed. For the cross-sectional verification, at least 14 centers returned the log files of 5 consecutive CI users for each of the major brands. For Neurelec 7 centers returned the log files. 79.5% of centers in the study provide implants to both children and adults, 17% to adults only, and 3.5% to children only.

Switch-On Procedures. On average, the CI processor is switched on after 28 days (QR: 21–30) with some centers starting after 2 weeks (Perth, Melbourne, and Chapel Hill) while one center only hooks up the processor after 6 weeks (Cambridge). All centers (100%) start with impedance measurements and if short or open most of them (60%) deactivate the corresponding electrodes immediately. Two centers (Brussels, Freiburg since 2013) systematically execute pure tone audiometry prior to switch-on to assess possible residual hearing, while another centre (Hannover) does this during the switch-on week (see further). Most, if not all, centers' focus goes to the setting of the minimum and the maximum current level of the electrodes. Med-El has a default THR level of 0 and 70% of centers do not change this. AB recommends setting the T level at 10% of the M level and 22% of centers do so. A majority of centers (55%) only determine either the minimum (31%) or the maximum (24%) level and make the other level depend on the first one. Forty-five percent of centers determine both the minimum and the maximum level behaviorally.

Determine Minimum Level Alone. If only the minimum level is determined, this is either done behaviorally (56%) or by means of intraoperative or postoperative eCAP thresholds (44%). Most centers (78%) only determine the minimum levels on a few electrodes and interpolate the values obtained to the other electrodes.

Determine Maximum Level Alone. Determining only the maximum level is restricted to Med-El and AB implants where the minimum level is then set at 0 or 10% of the maximum level. The maximum level is either determined behaviorally (71%) or by means of objective measures (eCAP in 29%, which is combined with or replaced by ESRT (electrically evoked stapedius reflex thresholds) in 14%). If objective measures are used, behavioral verification is done by half of the centers. Interpolation is used in only a minority of centers (29%) and so is loudness balancing (43%).

Determine Both Minimum and Maximum Level. Many centers determine both the minimum and the maximum levels and they all do this behaviorally. Only 15% of these combine this with eCAP measures. One center (Antwerp) has a particular way of using preset MAPs with minimum and maximum levels based on statistical analysis of MAPs which have provided good results in other recipients (Govaerts et al., 2010, Vaerenberg et al., 2011). Most centers (69%) measure the levels on a number of electrodes and interpolate the levels on the other electrodes. In some cases this can be as few as 3 electrodes (Southampton, Iasi), the results of which are then used to shift a preset profile towards the measured levels. Just after switching to

live mode, almost all centers (93%) increase or decrease the maximum levels based on the recipient's perception and some (45%) also shift the minimum levels.

Other MAP Parameters. Figure I.2-3.1 (a) shows that other MAP parameters are rarely modified from default during the switch-on session.

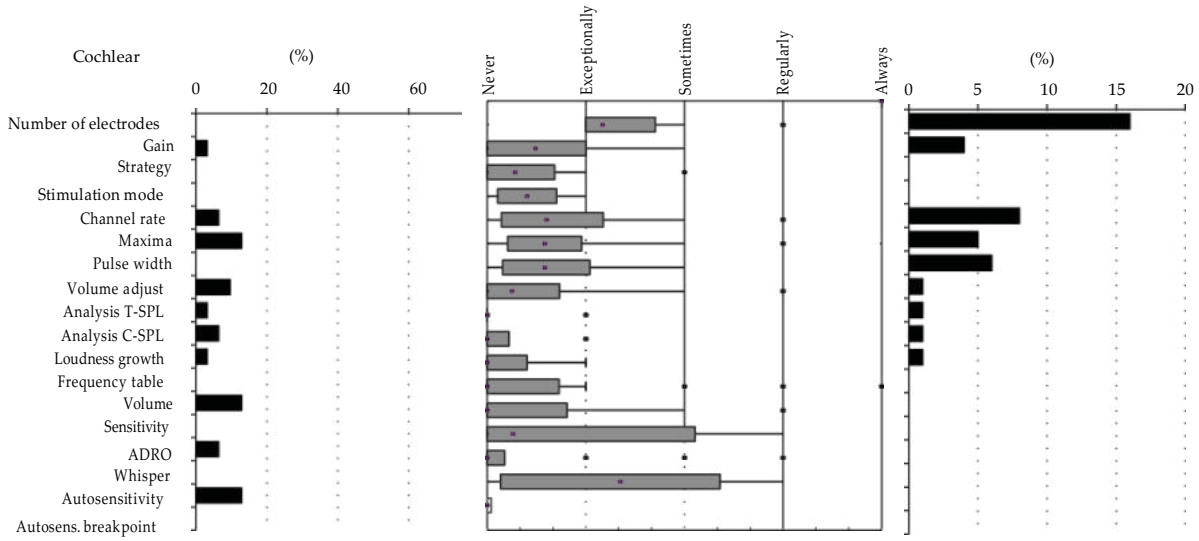
Cochlear. Thirteen percent of centers prefer more than the default 8 Maxima (9, 12 or 14) and 6% combine this with a higher than default Channel Rate (1200 pps). The Autosensitivity function is switched off by 13% of centers at switch-on. The Eargroup in Antwerp sets different Gains (statistically defined profile), and Analysis T-SPL (20), Analysis C-SPL(70) and switches off the ADRO function.

Med-El. With the Med-El device, 23% of centers start with a different strategy than the default FS4 strategy. Chapel Hill provides the patients with two strategies, HDCIS or FSP, which are the two strategies approved for use in the USA. Perth lets the patients chose between FS4 and FS4p and has experienced that 90% of recipients prefer FS4p. Paris-Avicenne gives FS4p as startup strategy and York, Paris-Beaujon, and Kansas City give FSP as start-up strategy.

Advanced Bionics. With the AB device a majority of centers overrule the default strategy (HiRes-P) and start with the HiRes-S strategy (72%), and of those, two-thirds select the Fidelity 120 strategy compared to one-third who stay with the default setting with Fidelity 120 switched off. This is in contrast to the centers who keep the HiRes-P strategy, of which 78% also keep the default setting with Fidelity 120 off. Some centers (20%) switch on Clearvoice systematically and some centers (30%) change the default Pulse Width setting of 10.8 μsec to either a higher value or to the automatic Pulse Width algorithm II (APW2). The default input dynamic range (IDR = 60 dB) is changed by 24% of centers.

Neurelec. The statistics of Neurelec's Digisonic device are not solid since they are derived from merely four centers, one of which (Southampton) only uses the binaural version. Half of them change the default number of maxima from 12 to 11 (Antwerp) or 6, depending on the duration of deafness (Southampton), and one center (Antwerp) switches the stimulation rate systematically from 600 pps to 500 pps and the preemphasis (egalisation de sonie) to −1.

Followup Procedures. After the switch-on session, all centers schedule a number of consecutive sessions to reach stable MAP settings. The average center schedules 3 sessions in the first quarter, 3 sessions in the following 3 quarters, and 1 annual session thereafter (see further). Attention goes mostly to the verification and adjustments of minimum and/or maximum levels to optimize loudness and almost half of the centers (46%) explicitly say that the followup sessions are roughly the same as the switch-on session.



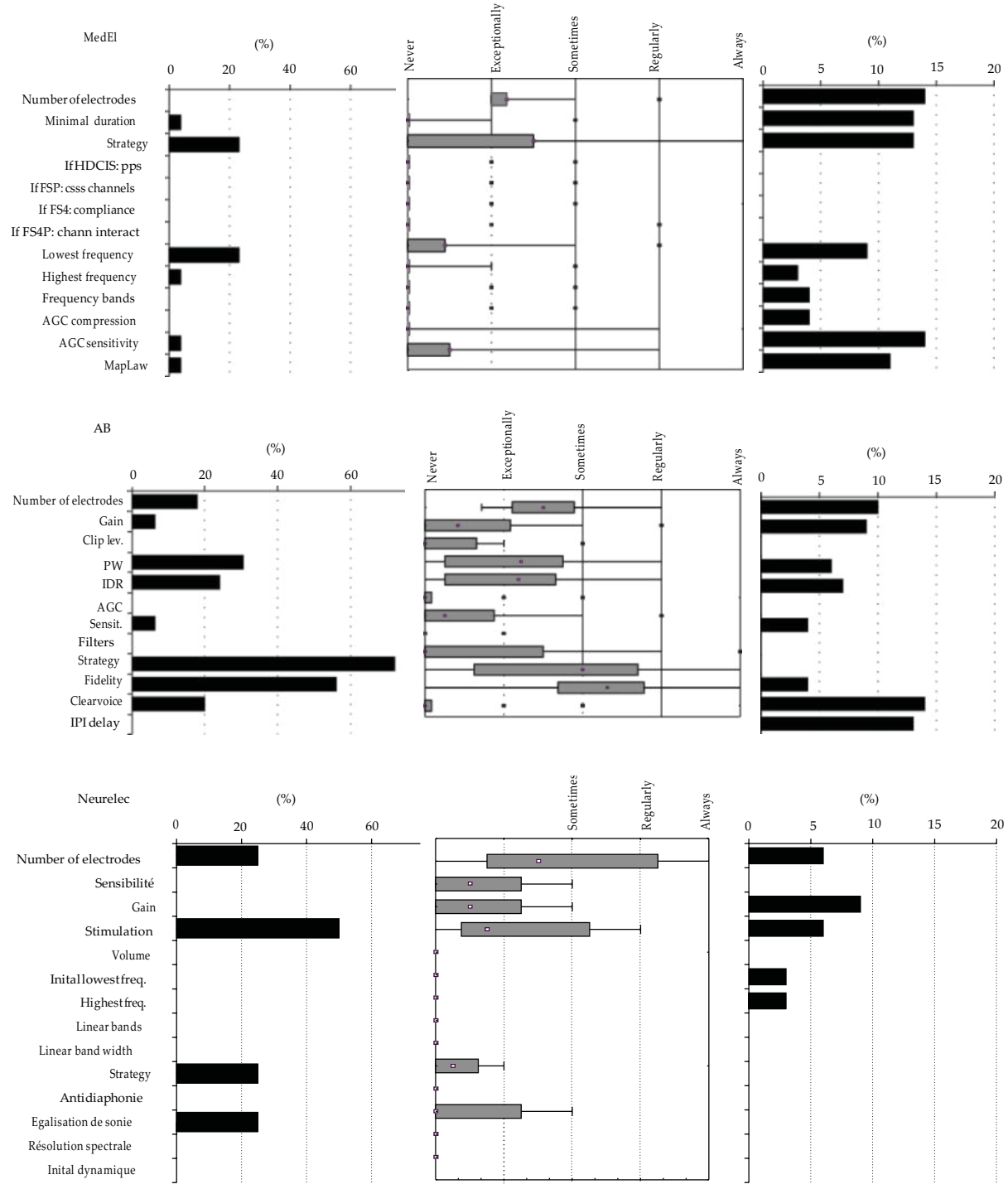


Fig. I.2-3.1: Occurrence of MAP changes for the 4 brands (Cochlear, Med-El, AB, and Neurelec). (a) The left panel shows the frequency of changing the default settings at switch-on, as retrieved from the questionnaire and the interview; (b) the mid panel shows the distribution of the frequencies of changing the MAP parameters during the followup sessions, as retrieved from the questionnaire and the interview (Box and Whisker plots with the central dot depicting the median value, the box shows the quartile range and the whiskers show the range); (c) the right panel shows the occurrence of MAP changes as observed in the cross sectional snapshot.

Adjustment of Minimum and Maximum Levels. All centers adjust maximum levels and many of them (61%) also adjust minimum levels. Global shifting of the maximum profile is

very common (96%) while tilting is done by less than half of the centers (39%). One centre lets the CI- user set and balance his/her own maximum level to most comfortable (Grenoble). All centers perform some kind of loudness balancing across individual electrodes and some centers perform pitch ranking (17%). Psychoacoustical tests (tonal audiometry, speech audiometry) or objective measures (eCAP, ESRT) are commonly performed (see below).

Adjusting Other MAP Parameters. Figure I.2-3.1 (b) shows that MAP parameters other than minimum and maximum levels are rarely modified. This is further illustrated by Figure I.2-3.1 (c) showing the cross-sectional observations. Deactivation of electrodes is one of the more common actions, but centers still report to doing this only every now and then (median response value is between exceptionally and sometimes, corresponding to approximately 10–15% in the cross-sectional data). Figure I.2-3.2 shows the reasons reported to deactivate electrodes. The most commonly reported reason is abnormal impedances, which is reported to occur "sometimes". Electrodes are also deactivated for other reasons such as when there is an indication of extracochlear location, if they cause nonauditory stimulation, uncomfortable perception or if they are inaudible, if the maximum levels are exceptionally high, or if tonotopical tests such as pitch ranking, channel separation, or spectral discrimination show unexpected results.

Cochlear. With the Cochlear device, the additional MAP parameter which is modified most, though still only exceptionally, is the Autosensitivity feature, which is then deactivated. In the cross-sectional data, also channel rate, number of maxima, and pulse width were modified in 5–8% of cases.

Med-El. With the Med-El device, the strategy is reported to be changed in "some" cases. Some centers change the default strategy (FS4 except in the USA) to FSP or FS4p in exceptional or some cases. One centre routinely sets the strategy to HDCIS in the primary program (Chapel Hill) and lets the patient choose between this strategy and FSP. This was confirmed in the cross-sectional data, which also showed that AGC Sensitivity, Minimum Duration, and MapLaw were changed in 11–14% of the cases and by many centers (36–79%).

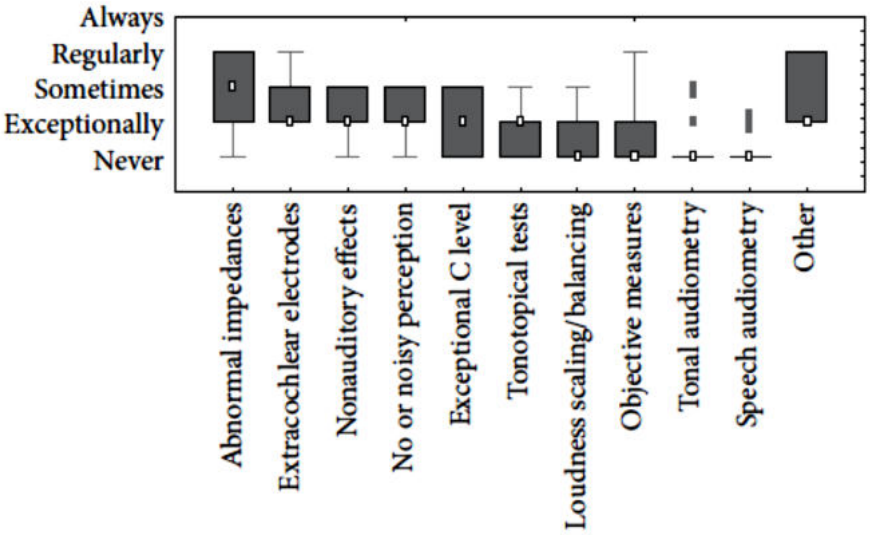


Fig. I.2-3.2: Alleged reasons for deactivating electrodes and the frequency they are reported to be really responsible for electrode deactivation in daily live.

Advanced Bionics. Advanced Bionics has more MAP parameters modified by a substantial number of centers in the course of the early followup period. The Clearvoice feature is activated sometimes to regularly (14% of cases in the cross-sectional study and 36% of the

centers), and also the Fidelity 120 feature is sometimes changed. This is confirmed by the cross-sectional data where these MAP parameters were only changed in 4–7% of the cases and by less than 25% of the centers. In the cross-sectional data the pulse rate was more often changed (IPI delay, 13% of cases, and 29% of centers).

Neurelec. Neurelec again has too few data to allow any reliable statements. The results are nevertheless included in the graphs for completeness.

Outcome Measurements. Figure I.2-3.3 shows that most centers report assessing subjective features and using them for fitting. Overall comfort (93%), auditory comfort (83%), and the presence of nonauditory sensations (83%) are used by most centers. None of the centers reports well defined and measurable targets for any of these features. Non auditory satisfaction, such as contentment, quality of life, implant use, are commonly assessed (87%) but only used by 41% of the centers to change the MAP settings.

Psychoacoustic measures are the only outcome measures for which a number of centers have well defined targets. This holds mainly for pure tone audiometry (85%) with targets set between 20 and 40 dBHL (median 30 dBHL, QR: 25– 35 dBHL). Spectral discrimination tests are used to drive the fitting by 41% of the centers of which 20% use well defined targets (either 100% if the A§E phoneme discrimination test (Govaerts et al., 2006) is used or 83–100% if Ling sounds are used). Speech audiometry in quiet or in noise are reported to be used to change the MAP parameters by 61% and 41%, respectively, but only 11% of the centers have set well defined targets and this is only for speech audiometry in quiet.

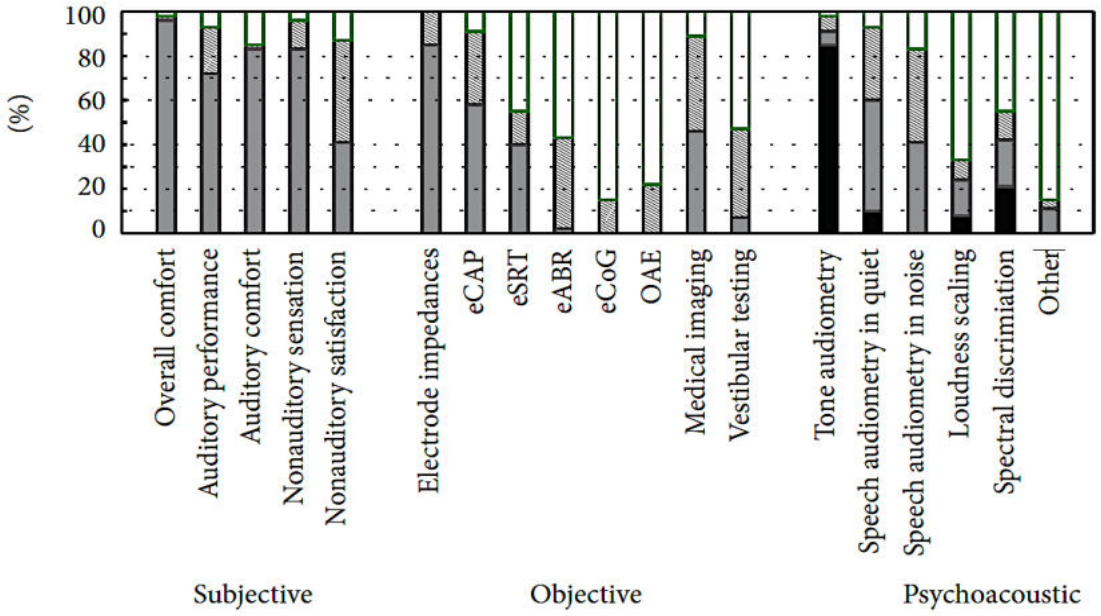


Fig. I.2-3.3: It shows the different outcome assessments which were enquired in the questionnaire together with the frequencies of the responses. The outcomes are grouped into 3 groups (subjective, objective, and psychoacoustic outcomes). The possible answers were (1) yes we assess this and use it to optimize the fitting (solid black and grey bars), (2) yes we assess this but for other reasons than steering the fitting, like for documentation or longitudinal followup (shaded bars), or (3) no we do not use to assess this (white bars). For the solid bars (assess and use it) a distinction was made into whether they have well defined targets to reach (black) or not (grey).

The cross-sectional data confirm that free field audiometry was performed in 60% of the cases, speech audiometry was performed in quiet in 45% of cases, speech audiometry was performed in noise in 19% of cases, loudness scaling was performed in 11% of cases, and spectral discrimination tests were performed in 15% of the cases.

Discussion

This report attempts to give an inventory of the current state of the art as it is based on a vast number of CI centers worldwide. All together they represent over 47000 CI recipients and 93% of the participating centers have more than 10 years of experience. 65% of the centers are European, which may cause a bias towards an overrepresentation of European habits. Altogether this is an unprecedented inventory and we believe that it gives a representative view on the current practices in CI fitting, which may be considered as the benchmark of CI fitting in 2013. A first observation is that most centers now offer 3 CI brands and perform cochlear implantation in both children and adults. This is different from years ago when many CI centers only offered one brand and only performed CI in adults. A second observation is that, despite the huge variability across centers (see further), some common practices can be extracted and they would seem to be as follows. The typical switch-on procedure takes one session comprising counseling and 1 hour of fitting. Testing is not performed at this stage. The fitting procedure is as follows: (1) connect the processor 4 weeks after surgery; (2) measure impedances and deactivate electrodes in case of short or open circuits; (3) measure the maximum level behaviorally on a number of electrodes along the electrode array, and interpolate the others; (4) set the minimum level at 0 for Med-El, 10% of M for AB; for the other implants measure the minimum level behaviorally on a few electrodes and interpolate the others; (5) perform loudness balancing by presenting a signal on all electrodes successively; (6) reduce the maximum level and switch on the micro- phone; (7) let the CI recipient accommodate for a few minutes and ask whether sounds, including loud sounds, are tolerated; increase or decrease the entire profile of maxima in order to make loudness tolerable or comfortable; (8) put a number of progressive MAPs in the processor; (9) instruct the patient to accommodate to each program for a couple of days and switch to the next one afterwards.

The typical first-year follow-up would comprise three monthly sessions followed by three quarterly sessions of one hour each. The sessions would typically look like this: (1) perform pure tone audiometry and speech audiometry (in quiet); (2) measure impedances and deactivate electrodes in case of short or open circuits; (3) verify the levels on individual electrodes by loudness balancing; (4) shift the profiles of the maximum and, if necessary, also of the minimum levels globally; (5) if deemed necessary, tilt the maximum levels globally; (6) define own criteria to identify selected and exceptional cases in whom other MAP parameters are modified.

It is remarkable to observe the substantial variability across centers and this holds for virtually all aspects of CI fitting and followup. Each CI center has its own policy in terms of timing, content, and methodology. The observation that some centers commonly activate the processor as soon as 2 weeks after surgery seems to suggest that 2 weeks may still be well within the safe time window (Henkin et al., 2006, De Ceulaer et al., 2003).

On average, CI recipients undergo one switch-on session followed by six fitting sessions in the first year, each taking approximately one hour of technical interaction (fitting and testing) plus a considerable amount of counseling time which has not been enquired in this survey. Behind this average there are huge between-centers differences. Most centers have one switch-on session followed by a take-home experience for accommodation. In the year following switch-on, some centers spend no more than approximately 1.5 to 2.5 hours (Paris-Avicenne, Casablanca, Ghent, Pune, Mumbai, Hannover, Berlin, Valencia, and Lyon) and one center schedules only 3 sessions (Warsaw), while other centers spend at least 12 hours (Las Palmas, Leiden, London St-Thomas, and Amsterdam) or as much as 15 sessions (Brussels). Almost all centers have as follow-up one session per year which takes between 1 and 2 hours of technical interaction (fitting and testing) with the CI user.

When it comes to the content of fitting and follow-up, most attention goes to the setting of minimum and maximum levels per electrode. Every center appears to have its own policy on

how to determine these levels. Behavioral assessment is commonly used, but, whereas this was performed for each individual electrode in the past, it now seems common to assess the levels on a few electrodes only and to deduce them by interpolation for the remaining electrodes (Plant et al., 2005). Evoked potentials (mainly eCAP thresholds) are used by an important minority of the centers, but they appear to be used as global indication of minimum or maximum levels rather than as strict anchor points. The levels set this way are preliminary anyhow, since they are shifted and to a lesser extent tilted in live mode, mainly based on subjective appreciation of loudness (Hughes et al., 2000). Whereas many reports correlate eCAP based MAPs with behaviorally based MAPs, as far as we know there are no reports claiming to improve speech understanding when eCAP based MAP optimization is carried out. On the contrary, Smoorenburg concluded that the applicability of eCAP measures in processor adjustment could not be demonstrated (Smoorenburg et al., 2002). Deactivating electrodes is the most frequent next MAP modification, although this remains rare.. The current survey demonstrates that centers have their own and often different methods to do so (Figure I.2-3.2). We have developed a uniform graphical representation for all four commercially available implant systems to clarify this behavior in the acoustical, electronic, and electrical domain (Vaerenberg et al., 2014) and we hope that the interactive application which has been developed to simulate the devices' behavior will be instrumental for clinical use. No scientific studies exist to explore a systematic impact of modifying parameters like the Input Dynamic Range, the Sensitivity, the AGC Compression factor, the MapLaw, and so forth. Hence, discussing the relevance of this can only be subject to speculation. Most centers agree on a target of 30 dBHL (±5 dB) for most audiometric frequencies, and this is achievable with current microphones and front-end processing.

Auditory performance, however, hardly depends on thresholds but rather on supraliminal sound processing. The core function of the cochlea is discriminating the different features of sound, such as loudness, spectral content, and temporal content, and it is striking to see that less than 50% of the centers report basing their fitting on measures to assess this and that less than 25% report having targets in this domain (Vaerenberg et al., 2014). Speech audiometry in quiet or in noise relates to the daily auditory performance but depends on more than just the cochlear processing of sound. Therefore speech audiometry is only partly indicative of the quality of cochlear functioning. Speech audiometry is used by approximately half of the centers but most use it to monitor performance, that is, to detect any undesired deterioration over time. Only 11% report having well defined speech audiometrical targets when it comes to CI fitting. This is in line with instructional literature which extensively explains the available methodology and how to use it to determine the minimum and maximum levels but which avoids mentioning measurable targets (Shapiro, Bradham, 2012, Wolfe, Schafer, 2010, McCormick, Archbold, 2003, Waltzman, Roland, 2006, Niparko, 2009). Shapiro coined the term "common lethargy" when referring to the CI audiologists' willingness to consider changes in device programming and he correctly stated that device programming is not a goal per se but the absolute goal is to provide the patient with a comfortable program which ensures maximum performance (Shapiro, Bradham, 2012).

Conclusion

In conclusion, it seems fair to summarize the current state of CI fitting as setting global profiles of maximum current levels and to a lesser extent of minimum current levels, mainly based on subjective feedback from the CI user. Many different approaches exist and in the absence of targets or well defined outcome measures it seems impossible to compare all these differences and to judge whether some yield better results or are more efficient than others. It is likely that several approaches in the hands of different experts may lead to similarly good results. It is equally likely that defining common measurable targets may be a next step to be taken towards the optimization of the art of fitting.

I.2.4. Research of the effectiveness of deafness treatment by cochlear implants and bone anchored hearing aids (BAHA)

Hearing loss is one of the health problems affecting about 10% of a country's population (Stevens et al., 2013). Depending on the degree of hearing loss, unilateral or bilateral damage, congenital or postlingual appearance of deafness, this pathology has a variable impact on the patient, but always lowers communication skills, reduces access to information and stigmatizes patients in society (Nordvik et al., 2018, Monzani et al., 2008, Niemensivu et al., 2015).

The most well-known and used implantable hearing aids devices are: cochlear implant for severe or profound hearing loss and bone-anchoring implantable auditory prostheses that are recommended for patients with mild or medium conductive and mixed hearing loss to stimulate the affected ear (Dun et al., 2011, Reinfeldt et al., 2015), but also for patients with single side deafness (SSD) (Stewart et al., 2011, Stenfelt, 2011) for cross hearing (contralateral hearing through bone conduction) (Kompis et al., 2011). The hearing implantable devices are used equally for adults and children. For the recommendation of hearing implanted devices in children there are discussions about the ethical side of the decision of implantation (Radulescu, Martu, 2007, Miziara et al., 2012).

In early stages of this technology, cochlear implantation was offered as a treatment to individuals with deafness that derived essentially no speech understanding from conventional amplification. As the evidence for enhanced speech recognition accumulated, coupled with technological advances, it became apparent that individuals with cochlear implants received benefits superior to those of many individuals with severe and profound hearing losses who used acoustic amplification (NIH Consensus, 1995).

I.2.4.1. The cochlear implant efficacy in patients with genetic sensorineural hearing loss

Background

At least 50% of all congenital sensorineural hearing loss are considered to be genetic and 2/3 of these are nonsyndromic, where the hearing loss is the only pathologic condition. About 80% of the genetic nonsyndromic forms sensorineural hearing losses are autosomal recessive transmitted (Petersen, Willems, 2006, Morzaria et al., 2004).

Regarding the syndromic deafness there have been over 400 forms described and the most common are: Waardenburg, Usher, Alport, Jervel and Lange-Nielsen, Norrie, brachio-oto-renal, Stickler, Pendred and Treacher Collins (Van Camp, Smith, 2020).

A big progress was made in 1997 when the first nuclear gene implicated innonsyndromic sensorineural hearing loss was discovered the gap-jonction-beta-2 gene (GJB2) (Kelsell et al., 1997). The mutations in the GJB2 gene on the DFNB1 locus on 13q12 are responsible for 50% of the cases of autosomal recessive nonsyndromic sensorineural hearing loss (Kenneson et al., 2002). In the last years there have been more that 70 mutations of the GJB2 gene discovered in patients with nonsyndromic sensorineural hearing loss (Cryns et al., 2004, Liu et al., 2005). The most frequent of these mutation in the European population is the 35delG mutation, having also a frequency of homozygous occurrence of over 60% (Cryns et al., 2004, Liu et al., 2005). The GJB2 gene encodes for connexin 26, a protein that forms intercellular gap junctions connecting the supporting cells in the cochleea.

Severe and profound sensorineural hearing loss have a great impact on communication skills. Whatever the cause of a severe or profound deafness that is not treatable by conventionally hearing aids, the only possible therapeutic solution remains the cochlear implantation (McPhillips, 2010). However, the implantation results may be different depending on the etiology of deafness. Even in genetic deafness, the results of cochlear implantation may vary depending on the gene involved and the population we are referring to.

Main articles published in this field:

- Mârțu Cristian, Olariu R, Manolache O, **Cozma S,** Rădulescu L. Tonal audiological performance evaluation after cochlear implantation in children with GJB2 gene related hearing loss. *Romanian Journal of Oral Rehabilitation.* 2011; 3(4): 8-11. ISSN 2066-7000

Scientific contributions /Clinical implications:

- Through our research, the results of hearing rehabilitation after cochlear implantation in a homogeneous group of children with genetic deafness affecting the GJB2 gene were evaluated for the first time in Romania. These results demonstrated the efficiency of the treatment of this type of deafness in children by cochlear implantation, consolidating in practice the program for deafness tratment by implantable auditory prostheses that we carry out in our hospital.

Aim of the study

In this study we evaluated the auditory performance by pure tone audiogram testing after unilateral cochlear implantation for children with GJB2 related mutations and to compare the results with the ones from children that did not show any mutations in the GJB2 gene. Because of the lack of statistic analysis and insufficient numbers in literature the evaluation of the auditory outcome of unilateral cochlear implanted GJB2 related sensorineural hearing loss represents a very useful tool for the counselling clinician and to help predict the auditory outcome before the cochlear implant surgery.

Materials and methods

Twenty-eight children with prelingual sensorineural hearing loss and unilateral cochlear implantation were randomly selected from a group of 95 patients, cochlear implanted in the ENT Clinic of the Clinical Rehabilitation Hospital Iasi. The genetic tests for the GJB2 mutations were carried out in accordance with the protocol, in the Department of Oto-Rhino-Laryngology, Head and Neck Surgery, University Medical Center Freiburg, Albert-Ludwigs University Freiburg, Germany. The study was approved also by the Ethics Committee of the Rehabilitation Hospital Iasi (No. 12511 10.07.2009). Informed consent was obtained from the patients, parents or legal guardians for children before collecting blood for genetic testing. We have organised 2 study groups: group A comprised 14 children with GJB2 related sensorineural hearing loss and group B comprised 14 children with sensorineural hearing loss without any mutations in the GJB2 gene. These two groups are comparable by sex, age and age of implantation. The tonal auditory performance with the cochlear implant was evaluated by free field pure tone audiogram. The tests were carried out by AA222 AudioTraveler audiometer and calibrated speaker system with Interacoustics preamplifier in the Audiology Department of the hospital.

Results and discussions

In this study we intended to research whether there is any difference regarding post-implantation auditory performances of the children from the two groups: group A with GJB2 related sensorineural hearing loss and group B with non-GJB2 related sensorineural hearing loss. The auditory outcomes in children after cochlear implantation can be influenced by early age of implantation (Tong at al., 2007), socioeconomic status (McDonald Connor, Zwolan, 2004) and etiology of hearing loss (Rajput et al., 2003). The cochlear implant works by directly stimulating the auditory nerve cells and the spiral ganglion cells (Clopton et al., 1980) with electric impulses. Studies on patients with GJB2 unrelated deafness have showed a smaller cellular population in the spiral ganglion (Jun et al., 2000). These patients can have other mutations in nonsyndromic deafness genes such as OTOF (Varga et al., 2003), GJB3 (connexin

31) (López-Bigas et al., 2001), KCNQ (Kharkovets et al., 2000) associated with pathologic changes in the auditory nerve of central auditory pathway.

We have determined the auditory tonal thresholds and we have calculated the average of these thresholds for the frequencies of 500, 1000, 2000 and 4000Hz. We have taken into consideration the first tonal thresholds that averaged at 35 dB or better for the given frequencies. The testing method was adapted according to the age of the cochlear implanted child and we used the subjective audiometric method as well as the visual reinforcement audiometry. The auditory rehabilitation protocol used by our clinic offers successive fitting sessions after activation at 1, 3, 6, 9, 12, 18 and 24 months and then yearly.

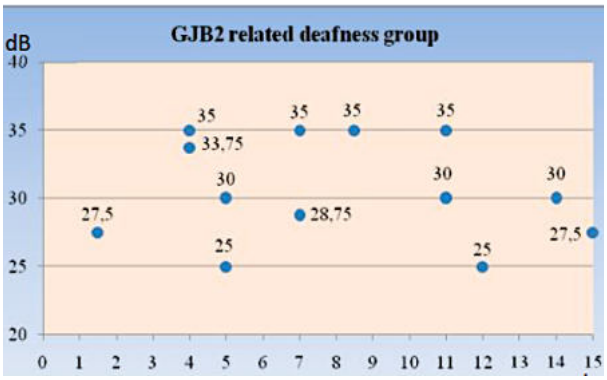


Fig. I.2-4.1. Free field PTA average threshols for GJB2 patients - distribution in time (months)

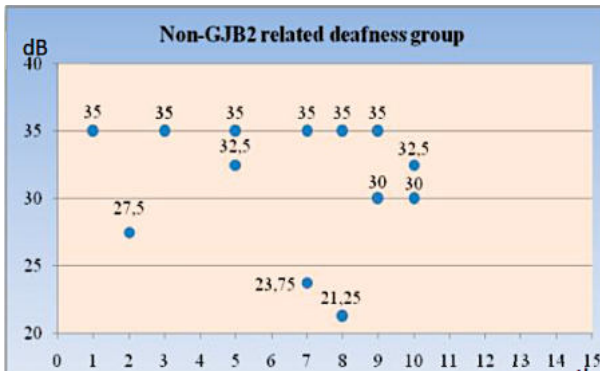


Fig. I.2-4.2. Free field PTA average threshols for non-GJB2 patients - distribution in time (months)

The evaluation of the free field auditory performance with the cochlear implant was not possible after every fitting session because of several issues: the age of the child, the child may become tired or may present lack of collaboration. After analyzing the data provided by the audiologic testing we have found out that the group of GJB2 related sensorineural hearing loss had reached the first average tonal threshold of 35dB or better in a longer period of time from the implant activation, as presented in Fig. I.2-4.1. We have found a relatively wide time frame to reach the required average after activation, ranging from 1,5 months to 15 months. The values of the averages of the tonal thresholds of the free field audiometry were found between 25 dB and 35 dB. In the group of children with non-GJB2 deafness, the average free-field tonal thresholds of at least 35 dB were found to be obtained in a shorter period than in the GJB2 group, between 1 and 10 months after the cochlear implant activation (Fig.I.2-4.2). In contrast to the first group, we can observ that the values of the averages tonal thresholds are less evenly distributed, few of them being even less than 30dB.

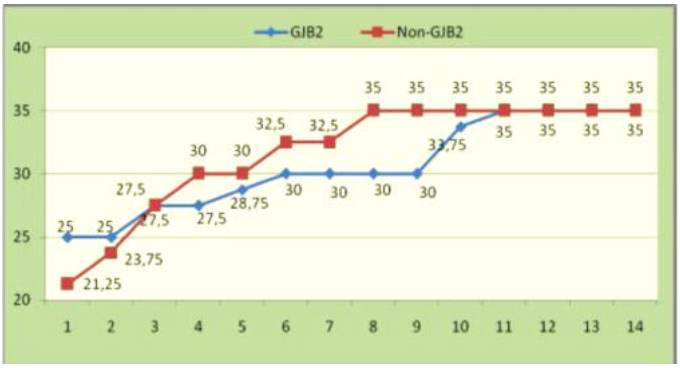


Fig. I.2-4.3. Average tonal threshold values distribution in time for GJB2 and non-GJB2 patients

Fig. I.2-4.3. shows clearly that the GJB2 related deafness group (shown in blue line) has a lower overall average of the tonal thresholds (30,51 dB) and thus reaching a better conversational tonal hearing faster than the non-GJB2 (shown in red line) related sensorineural hearing loss group (average of 31,60 dB). The results we found are in accordance with studies that have examined GJB2 related sensorineural hearing loss (Sinnathuray et al., 2004, Bauer et al., 2003, Fukushima et al., 2002, Matsushiro et al., 2002, Green et al., 2002). However some studies found no difference between the two groups (Dahl et al., 2003, Cullen et al., 2004, Taitelbaum-Swead et al., 2006, Lustig et al., 2004). This might arise partially from the fact that some of these studies have small sample sizes of patients, lack of proper statistically analysis or shorter follow-up period.

Conclusions

Our study indicates that the group of children with GJB2 genetic deafness achieves conversational hearing levels with cochlear implant better and earlier than children with other etiologies of deafness. This evidence suggests that shortening the waiting time to cochlear implantation of children with deafness of non-genetic causes would be a factor in improving their auditory-verbal performance, along with speech therapy and family care.

I.2.4.2. The binaural cochlear implantation – a special type of deafness treatment for adults

Background

The concept of bilateral implantation appeared with the results of comparative studies performed in patients with normal hearing or with conventional hearing aids versus unilateral implant (monaural), when the disadvantages of monaural hearing in everyday life were highlighted (Clark, 2003). At the same time, several research groups have proven and described the phenomena of neurological maturation and plasticity of the auditory neural system, phenomena possible only under characteristic sound stimulation (Cozma, 2008, Lim, Anderson, 2006, Vincent et al., 2002). Binaural implantation, ie the use of a single device for both ears, is a possible solution for adult patients with profound bilateral sensorineural hearing loss, with lower costs.

1) *Normal binaural hearing.*

In subjects with normal binaural hearing, as opposed to monaural hearing, there is an effect of increasing the sensation of sound by 3 dB at the threshold and by 10 dB at over 30 dB, an essential increase for sound source localization in space, in order to suppress echoes and for hearing in a noisy environment.

2) Binaural hearing through the cochlear implant.

Binaural implantation is a possible solution in adult patients with bilateral profound sensorineural deafness, with lower costs. Binaural cochlear implantation has the advantages of stereo hearing compared to unilateral cochlear implantation, facilitating better and more natural understanding and localization of sound (Zwislocki, 1985, Dallos, 1992).

This type of unique cochlear implant, Digisonic SP Binaural, is a therapeutic alternative of major interest with an important impact on the patient's social life, representing a favorable prognostic factor in the evolution of the patient's hearing. (fig. I.2-4.4).

Main articles published in this field:

- Mârţu C, **Cozma S**, Rădulescu L, Mârţu D. Binaural cochlear implant-good choice in the treatment of deep sensorineural hearing loss. *The Medical-Surgical Journal.* 2011; 115(3): 826-33.

Scientific contributions /Clinical implications:

- The binaural cochlear implant was implanted for the first time in Romania in the ENT clinic in Iasi, constituting a revolutionary model that allows hearing with both ears using a single device. This device opened to us special study perspectives regarding the research of the processes of auditory rehabilitation through electrical stimulation, especially the process of reintegration of the stereophonic hearing and auditory localization.

Aim of the study

The study aims to evaluate the advantages of binaural implantation and monitor, record and analyze the evolution over time of tonal hearing and speech perception in quiet and noisy environment, in correlation with the phenomena of brain plasticity and patient adaptability to sound environment. Consequently, these advantages inherently lead to an improvement in the quality of life of implanted patients.

Materials and methods

We included in the study 3 patients with bilateral cochlear sensorineural hearing loss and with intelligibility below 50% at 60 dB SPL with hearing aid and without lipreading. Patients were implanted with the Digisonic SP Binaural implant. The external part consists of a single sound processor equipped with ipsilateral microphones and a contralateral auxiliary microphone. The receiver/stimulator has a short electrode holder for the ipsilateral cochlea and a long electrode holder for the contralateral cochlea, made specifically to reach under the scalp to the mastoid opposite the receiver/stimulator. (fig. I.2-4.5). The sound processor is able to process 2 stereo signals at the same time, the left-right processing can be done independently. During the study, several audiological tests were performed according to the established protocol: pre-operative, on the date of activation, 3 months and 6 months after activation. The hearing on each ear was tested, and then the binaural hearing, in the room with sound attenuation, with calibrated equipment (Interacoustics audiometer, preamplifier, 5-speaker system located in a semicircle and implant adjustment system).

Free field pure tone audiometry was performed for the right ear, left ear and both ears at 250, 500, 1000, 2000 and 4000 Hz frequencies to evaluate the auditory performance of pure tones through the cochlear implant. The speech audiometry curve was recorded, identifying the intelligibility threshold by presenting lists adapted to 10 standardized bisyllabic words at intensities of 60 and 70 dB SPL (in a quiet environment and in a noisy environment) (Cozma, 2009). Because the binaural implant restored stereophonic hearing, we followed the evolution of patients' performance on identifying the sound source localization. The tests were performed in a soundproofed cabin, using the system of 5 speakers placed on a semicircle in front of the patient: 1 and 2 on the right (90° and 45° respectively), box 3 in front (at 0°), and speakers 4 and 5 to the left (45° and 90° respectively).

The spatial distribution of the speakers aims to identify by the patient the direction from which the sounds are emitted. The speakers are calibrated and the signal is output via a calibrated signal amplifier, connected to the audiometer.

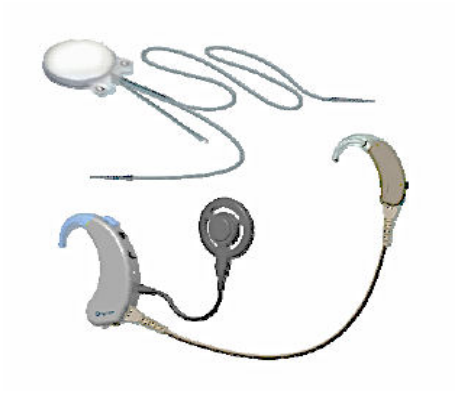


Fig. I.2-4.4. Cochlear Implant *Digisonic SP Binaural*

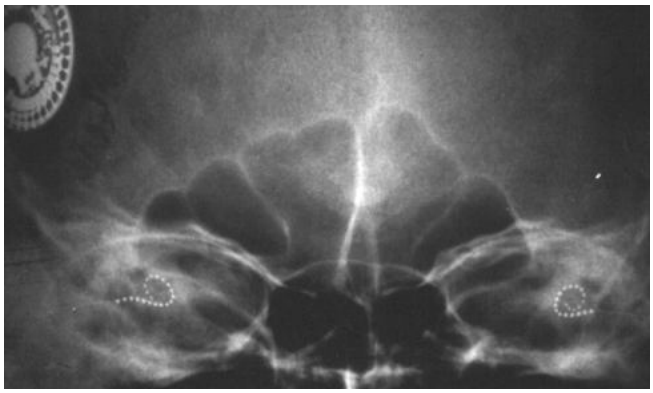


Fig. I.2-4.5. Imaging aspect of binaural implant positioning (receiver/stimulator and the two intracochlear electrode arrays)

The stimulus is a white noise presented at the intensity of 65 dB SPL. For each patient was used a testing algorithm that included 10 tests for each speaker, issued randomly, so a total of 50 stimuli for which the patient had to identify the direction from which it was presented.

Results and discutions

In the case of pure tone audiometry, a significant decrease in the value of auditory thresholds recorded from activation can be observed up to 6 months after this, so an improvement in tonal perception for each ear (right-red, left-blue), but especially for binaural hearing (green) (fig. I.2-4.6).

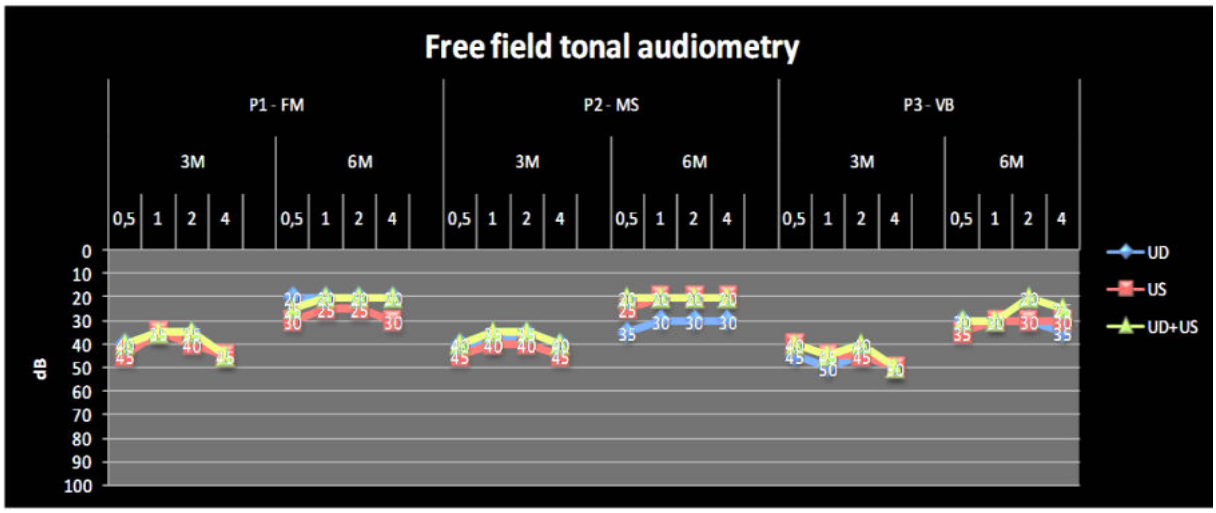


Fig. I.2-4.6. Results of pure tone audiometry (Right Ear, Left Ear, Right Ear + Left Ear)

The hearing level at the time of testing both ears is for the first 2 cases tested (P1 and P2) at the maximum hearing level recorded by the patient with any individually tested ear, and in the case of patient P3 the hearing thresholds for the 2 ears tested simultaneously (at 6 months) are even lower (for the 2000Hz and 4000Hz frequencies) than the thresholds recorded on any individually tested ear, so hearing improved considerably from the adjustment and control session 3 months after implantation and then at 6 months in all patients.

In the case of speech discrimination at 60 and 70 dB SPL in silence, the results recorded 6 months after activation compared to those recorded at 3 months are similar for the first patient

(P1). We can observe a better word recognition at 60 dB SPL when testing binaural hearing than testing for each ear. In contrast, patient P2 showed a significant improvement at 6 months in word recognition both for each ear, but especially in binaural testing. Also, the results in testing both ears at the same time were better than in the case of testing each ear separately. This pattern of evolution is similar to most binaurally implanted cases that we have analyzed in communications in the literature (Zheng et al., 2011, Hancock et al., 2010). In the last tested patient, there was an improvement in hearing for the right ear from 3 months to 6 months but no obvious progress for the left ear. The performance of the 3-month binaural test was at the level of the hearing recorded with the right ear at the same time. When testing both ears at 6 months at 60 dBSPL, there was an improvement in the word recognition score, but not up to the level reached by the right ear. (fig. I.2-4.7).

We can observe that when testing from 6 months after the moment of activation, in the case of all patients, the recruitment phenomenon is registered by decreasing the word recognition score at the intensity of 70 dB compared to 60 dB. In the case of 3-month testing we can observe the recruitment phenomenon for patient P1 for each test, and for patient P2, the phenomenon appeared only at the time of separate testing of each ear.

For the speech audiometry in a noisy environment (white noise with an intensity of 60 dB) for speech discrimination at 60 and 70 dB SPL we can see the lack of response at 3 months and 6 months from the patient P1. For the P2 patient, binaural hearing may be observed as good as for the best tested ear (right ear) 3 months after activation and an improvement in recognition at 6 months, compared with testing at 3 months for each individual ear tested as well as for both simultaneously tested ears. In contrast, binaural hearing at 6 months recorded an improvement in the recognition scores of the best tested ear (right ear) for both the intensity of 60 dB SPL and 70 dB SPL. In the case of this patient, we observed the appearance of the recruitment phenomenon at the 3 months test after the activation of the binaural cochlear implant for the right ear.

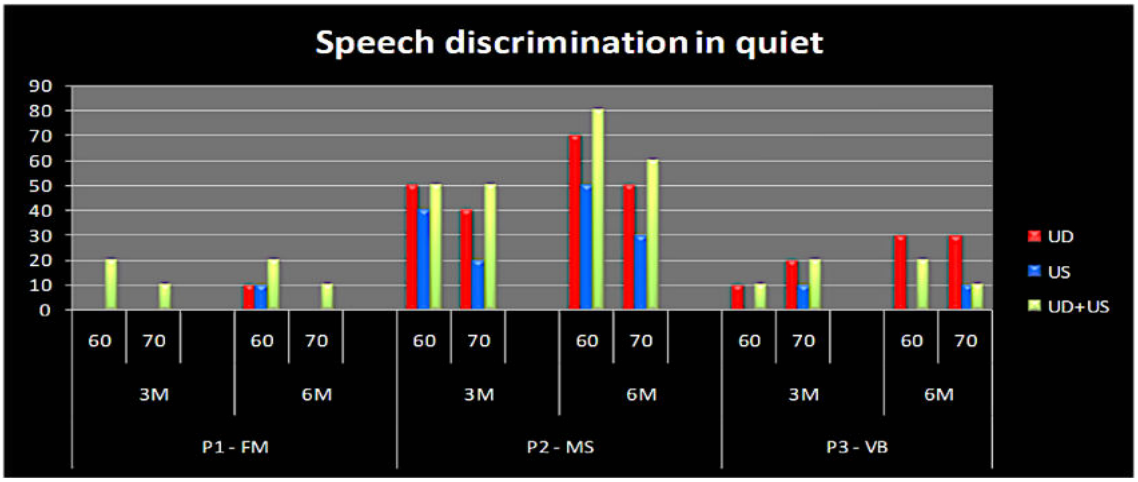


Fig. I.2-4.7. The results of speech audiometry in quiet environment
(Right Ear, Left Ear, Right Ear+Left Ear)

For the P3 patient, there was an improvement in recognition scores at 6 months compared to the test at 3 months for hearing with both ears simultaneously and a stationary for the left ear for both intensities tested. For the right ear, no response was obtained at 60 dBSPL for both test moments, but there was an improvement at 6 months for the intensity of 70 dBSPL, the recognition score being even higher than in the case of binaural hearing (fig. I.2-4.8).

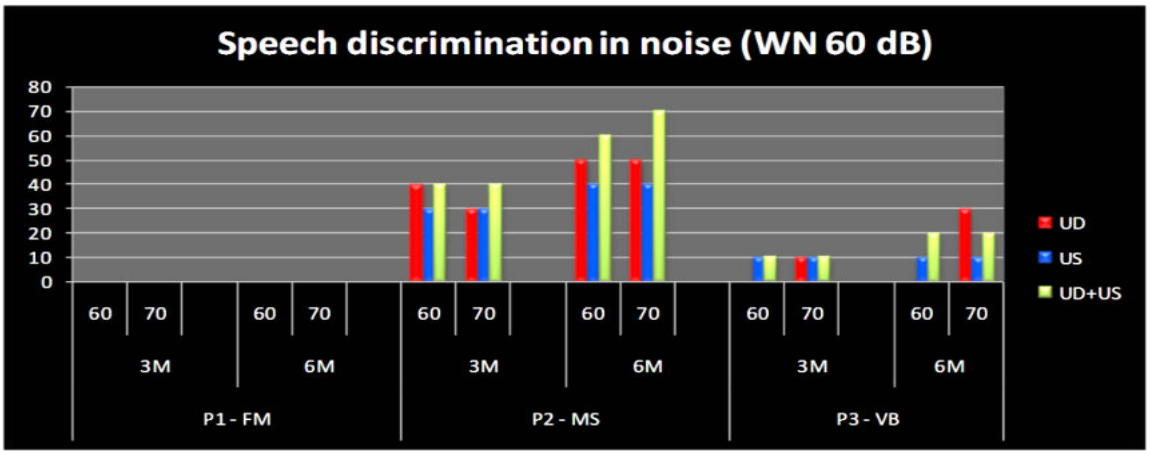


Fig. I.2-4.8. The results of speech audiometry in noisy environment (Right Ear, Left Ear, Right Ear+Left Ear)

In the case of localization tests with 5 speakers and white noise of 65 dBSPL, a good sound origin localization was observed to the right when stimulating the right ear and a good sound origin localization to the left when stimulating the left ear (fig. I.2-4.9).

For binaural stimulation, localization occurs with less accuracy, but with good results for lateral localization on each side. For the sounds presented from the front speaker, the location was weak, but more accurate than in the case of individual stimulation on each ear. The noise source locatization in the binaural hearing from the initial test after 3 months from activation to 6 months has improved in all patients tested, both for the localization of the lateral speakers but especially for the localization of the speakers in the fronto-lateral area.

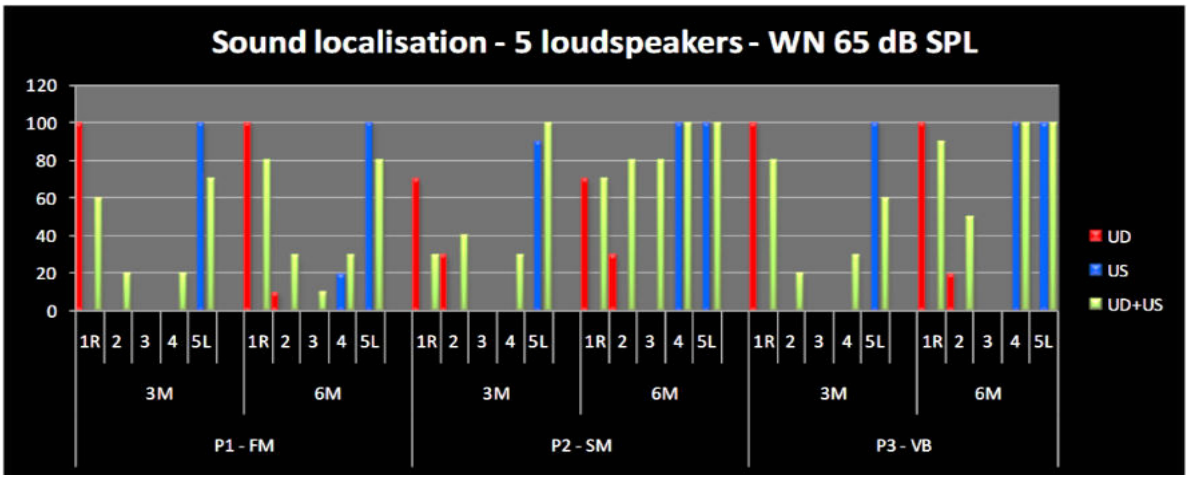


Fig. I.2-4.9. The results of sound localization (Right Ear, Left Ear, Right Ear+Left Ear)

From the data recorded during the study of pure tone thresholds we noticed that binaural hearing allows the detection of lower thresholds or at least equal to the thresholds obtained in the case of monaural hearing and we noted an evolution over time to lower hearing thresholds from 3 months to 6 months. We also noted a progress in 6-month testing compared to 3-month post-activation testing in terms of speech discrimination in both quiet and noisy environments in the case of binaural hearing testing for P2 and P3 patients.

For localization tests, there was an improvement in the sound source localization (both for the side speakers but especially for the center speakers) in binaural hearing at 6 months testing compared to 3 months after activation testing in tested patients. This fact indicates an

evolution in time towards the hearing as close as possible to the stereophonic natural one and can be explained by the neural plasticity and adaptability phenomena.

Conclusions

The binaural cochlear implant consisting of a single sound processor, a single receiver-stimulator and 2 electrode arrays, is a less expensive alternative, with better temporal accuracy between the 2 ears and with a shorter surgical time than implantation. bilateral. Binaural cochlear implantation has the advantages of stereophonic hearing, facilitating the speech understanding in silence and especially in noise, favoring the sound localization, and through all this it facilitates communication and increases the quality of life.

I.2.4.3. The bone anchored hearing aid in deafness treatment – assessment of patient's performances

Background

The bone anchored hearing aid (BAHA) is part of the implantable auditory prosthesis group and is recommended mainly for conductive and mixed hearing loss with good cochlear reserve, but also for neurosensorial profound unilateral deafness with normal contralateral hearing, where, through the transcranial effect, BAHA restores the integrity of the auditory field. Patients who can not benefit from conventional hearing aids have access to implantable prosthetic solutions which are primarily designed for the degree of hearing loss but also for other medical criteria such as the need for local administration of drugs through implantable devices (Pirlich et al., 2017, Martu et al., 2016).

Main articles published in this field:

- Bitere Oana, Martu Cristian, Olariu Raluca, Cobzeanu Bogdan, Martu Dan, **Cozma Sebastian**. Functional Results in Patients with Bone Anchored Hearing Aid. *Proceedings of National Romanian ENT, Head and Neck Surgery Conference.* 2018: 75-81.
- Oana Bitere, Luminița Rădulescu, Roxana Șerban, Corina Butnaru, Cristina Hera, **S. Cozma**. Proteza BAHA în surditatea unilaterală. *The Medical-Surgical Journal.* 2018; 2(s.1): 132-142. ISSN: 0048 - 7848

Scientific contributions /Clinical implications:

- The indications for the implantable prosthesis with BAHA system are varied, and the research of the performances obtained in the implanted patients represents a clinical confirmation of the efficiency of these devices. The research results bring valuable information for the national program in the hearing loss rehabilitation by implantable prostheses, justifying the costs of this type of treatment in patients who need intervention through the program.

Objectives

The aim of the study was to evaluate the effectiveness of the BAHA in a group of patients with different types of hearing loss, implanted and activated in the Clinical Rehabilitation Hospital in Iasi. We define as efficient rehabilitation the close to normal tone hearing aided by the BAHA device, auditory thresholds in the range of 20-30 dB for the communication spectrum frequencies (500 to 4000 Hz) and the utility of the device in

communication by assessing the aided speech discrimination. The objectives pursued were: selection of patients who have been activated for at least 6 months (in order to have a consistent result of device's efficiency without the risk of incompletely osteointegration of the implant) and statistical analysis of the patient population; analyzing the individual results, related to hearing loss on the implanted ear; evaluation of the efficiency of BAHA device in patients with unilateral deafness at which the prosthesis was indicated for cross hearing.

Methodology

The retrospective study included 30 patients with implantation age between 5 years to 63 years old, with an average of 29, diagnosed with mild or medium conductive or mixed hearing loss or neurosensorial profound unilateral acquired hearing loss and auditory rehabilitated by BAHA device between 2014 and 2017. The post-implant auditory protocol assesment included the determination of the pure tone auditory thresholds and the speech intelligibility in free field aided by BAHA devices. For diagnostic audiometry and also for postoperative evaluation we used the digital audiometer Affinity, from Interacoustics, Denmark, in a soundproof room, after the prior training of the patient. For pure tone audiometry, we tested the air conduction by supraaural headphones and the bone conduction by bone vibration using a warble tone on 250, 500, 1000, 2000, 4000 and 8000 Hz. For unilateral hearing loss patients, we used the masking strategy for healthy ear according to standards. The speech audiometry was performed by air conduction and bone conduction preoperatively and postoperatively in free field using calibrated loudspeakers. We used lists of disyllabic words from clinically validated test materials for Romanian language (Cozma et al., 2016). For evaluation of aided hearing with BAHA in free field, we used the masking strategy for contralateral ear (40 dB white noise presented by insert earphones). The results were stored in the system database and the data was then processed in the Excel program.

Results and discussions

The etiology of the hearing loss was otospongiosis in one case, malformation in seven cases, chronic otomastoiditis in four cases, sudden hearing loss in seven cases and unknown in eleven cases. Depending on the etiology of deafness of the patients included in the study, the audiological evaluation of the hearing (pure tone audiometry or auditory steady state response for children) we indentified different types of hearing loss (neurosensorial, conductive and mixed) represented in Fig. I.2-4.10.

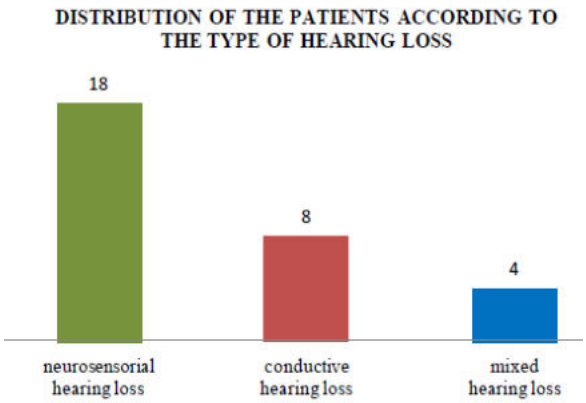


Fig. I.2-4.10. Distribution of the patients according to the type of hearing loss

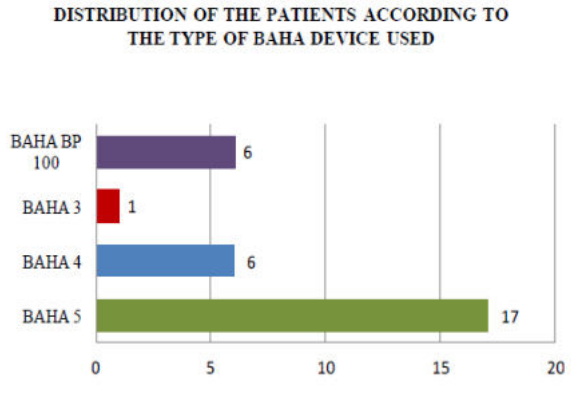


Fig. I.2-4.11. Distribution of the patients according to the type of BAHA device used

Subjects who participated in the study were implanted with four different types of BAHA devices, different technological generations: BAHA BP 100, BAHA 3, BAHA 4 and BAHA 5 (Fig. I.2-4.11).

Most patients were fitted with the latest generation BAHA 5 sound processor. The titanium implants of BAHA devices did not show any local complications during the time they were used, from surgery to the study period. BAHA device was indicated for ipsilateral stimulation in 18 subjects of the study group and for contralateral stimulation in 12 patients.

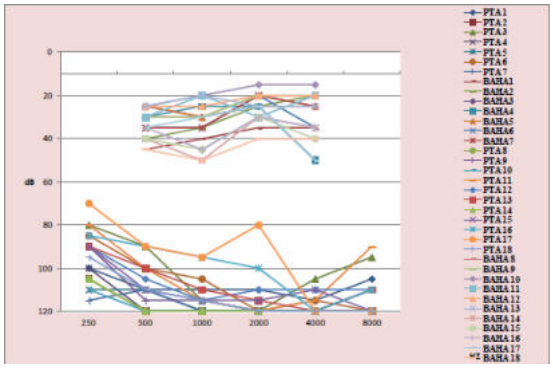


Fig. I.2-4.12. The individual pure tone audiometric thresholds of the deaf ear and the audiometric gain with BAHA device in free field for single side deafness patients

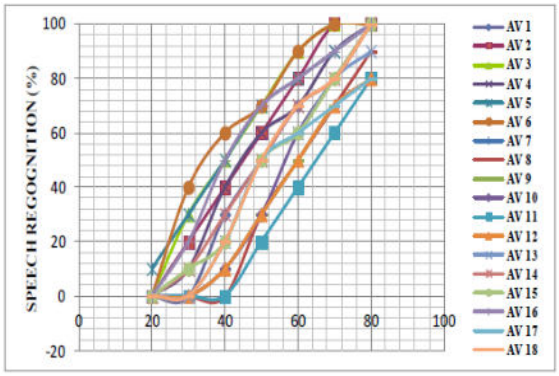


Fig. I.2-4.13. Individual scores for BAHA-aided free-field speech intelligibility in single side deafness

The auditory performances of patients with BAHA are presented for 3 study subgroups: patients with profound unilateral neurosensory hearing loss and quasi-normal contralateral hearing; patients with hearing loss caused by external and middle ear malformations; patients with suppurative chronic otitis and degenerative otitis (otospongiosis).

In Fig. I.2-4.12 are represented hearing levels of pure tone audiometry for the deaf ear in patients with unilateral profund hearing loss comparing with the BAHA aided thresholds in free field (cross hearing effect). The average audiometric thresholds for 12 patients with profound single side deafness comparing to the average pure tone BAHA aided tresholds in free field were between 20 and 45 dB, depending on the physical characteristics of the cranial mass and the fitting parameters. The average free-field hearing thresholds are: 33 dB for 500 Hz, 33 dB for 1000 Hz, 25 dB for 2000 Hz, and 31 dB for 4000 Hz.

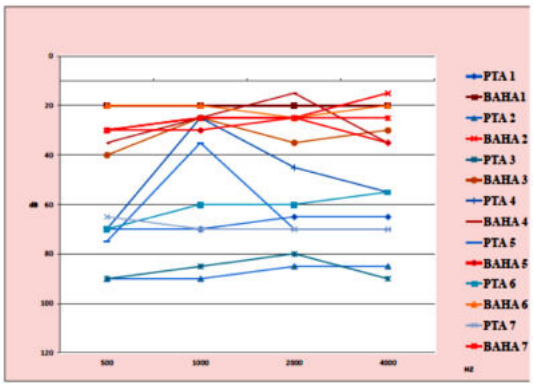


Fig. I.2-4.14. Individual pure tone audiometric thresholds and BAHA aided audiometric gain for patients with ear malformations

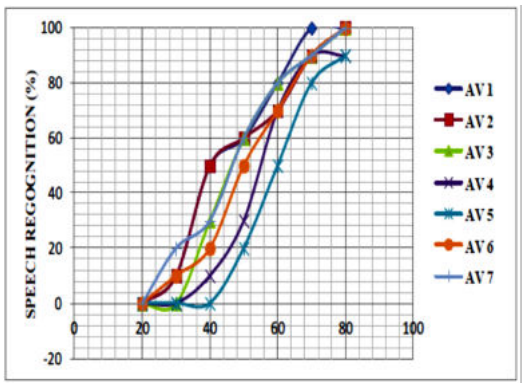


Fig. I.2-4.15. Individual BAHA aided speech recognition scores for patients with ear malformations

Regarding the speech recognition by BAHA device in patients with unilateral neurosensorial profound hearing loss, we obtained scores between 80 and 100% (Fig. I.2-4.13).

The average value for the maximum speech recognition score with BAHA device was 93%.

Based on the analysis we can state that the use of the BAHA device in unilateral deafness with normal hearing on the opposite ear brings the expected performance in terms of the auditory thresholds on all frequencies tested by BAHA, as well as for the speech recognition by crosshearing, the results agreeing with different other published studies (Stewart et al., 2011, Newman et al., 2008, Boleas-Aguirre et al., 2012, Wazen et al., 2010). In the group of patients with malformative pathology with conductive hearing loss, the analysis of the results showed that the BAHA prosthesis offers very good performances, allowing recovery of the ipsilateral auditory deficit (Fig. I.2-4.14). The individual scores and also the mean score for maximum level of speech recognition obtained with BAHA device in patients with external ear malformations were between 90 and 100% as shown below in Fig. I.2-4.15.

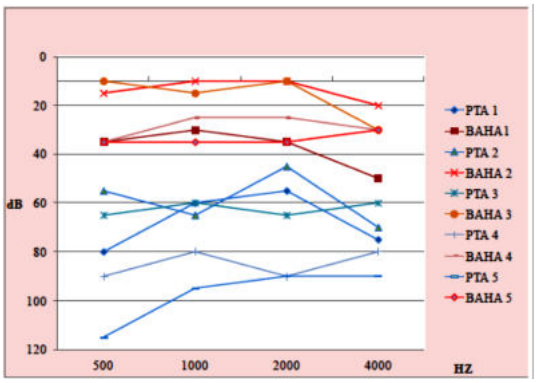


Fig. I.2-4.16. Individual pure tone audiometric thresholds and BAHA aided audiometric gain for patients with chronic otitis media and otospongiosis

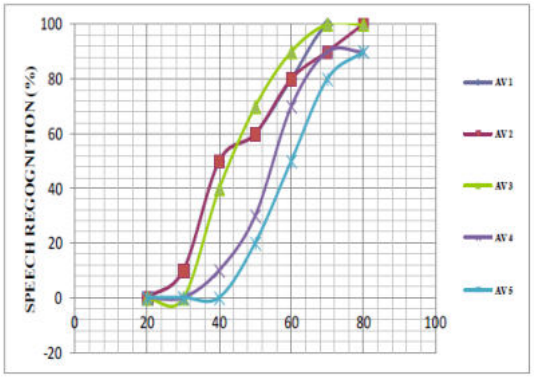


Fig. I.2-4.17. Individual BAHA aided speech recognition scores for patients with chronic otitis media and otospongiosis

The results of patients with conductive or mixed hearing loss caused by infectious (chronic otomastoiditis) or degenerative pathologies (otospongiosis), who received BAHA for ipsilateral stimulation show also an excellent hearing rehabilitation. Fig. I.2-4.16 presents the individual pure tone audiometry thresholds and the audiometric gain with BAHA device in free field for patients with chronic otitis media and otospongiosis, with an average for aided thresholds of 25 dB, a significant gain with the device. The speech recognition score obtained with BAHA for the third subgroup of patients is graphically represented in Fig. I.2-4.17, with a maximum intelligibility of 90-100%. The average of speech recognition scores obtained with BAHA in patients with chronic otitis media and otospongiosis was 93%.

Conclusions

The BAHA device has been shown to be an effective hearing aid in each case, for all types of pathology from our research subgroups (unilateral profound hearing loss, conductive or mixt hearing loss induced by malformative, degenerative or infectious chronic diseases), proving close to normal parameters for tonal and speech recognition audiometry. In this regard, if the device's indication is respected, the auditory gain obtained may be very satisfactory, allowing almost full recovery of hearing deficiency. In our study group there was no evidence of abandoning BAHA prosthesis and none postoperative local complication.

I.2.5. Cochlear implantation in rare inner ear diseases

Background

The cochlear implant, used for the treatment of severe and profound deafness, is the only indication if the etiology of deafness is associated with anatomical damage to the inner ear and cochlear space, such as cochlear or labyrinthine tumors, traumas with temporal bone fractures affecting the cochlea or various types of cochlear malformations. This pathology generally raises special problems regarding the cochlear insertion of the electrode array, the audiological results depending on the quality of the insertion. In the case of tumor, a particularly important element is the removal of the tumor with the preservation of tissues that allow the placement of the electrode, but also to limit or prevent a tumor recurrence. Researches on treatment and hearing rehabilitation strategies by cochlear implantation in many cases considered at the limit of the indication are welcome, and favorable results represent a valuable precedent for many clinicians teams in treating these rare cases.

I.2.5.1. Research for customized cochlear implant solutions in cases of inner ear tumors

Introduction

Hearing rehabilitation with cochlear implants (CI) has shown to be effective even after substantial trauma to the cochlea due to removal of intracochlear schwannomas via subtotal cochleoectomy (Aschendorff et al., 2017, Plontke et al., 2020, Plontke et al., 2018a). During removal of intracochlear tumors, the delicate structures of the modiolus with the spiral ganglion cells in Rosenthal's canal need to be preserved to enable sufficient stimulation conditions (Plontke et al., 2020). Thus, there is no safety margin ensuring complete tumor removal. Consequently, tumor growth may result from possible residual tumor cells within the remnants of the spiral osseous lamina and/or the modiolus. In patients with transmodiolar or translabyrinthine tumor growth but a need for hearing rehabilitation, tumor cells will naturally remain in the modiolus and internal auditory canal (IAC) after removal of the intracochlear portion of the tumor. Although these cases are rare, some patients will favor this approach, if hearing rehabilitation has priority for the patient over complete tumor removal or if it is the only remaining chance for hearing rehabilitation if the contralateral side is already deaf (Carlson et al., 2016, Rahne T et al., 2019).

Follow-up with magnetic resonance imaging (MRI) is thus required to assess growth of possible or obligate residual tumor cells. The inner ear and the IAC can be left out from the MRI artifact area of the magnet's receiver coil if the coil is placed further posterior and superior than in standard CI surgery (Schroder et al., 2018, Tam et al., 2020, Todt et al., 2017). In addition, a CI model should be chosen with a high compatibility of the magnet in the receiver coil. Otherwise, complications such as magnet dislocation and pain may occur (Grupe et al., 2017, Leinung et al., 2020, Shew et al., 2019, Tam et al., 2020, Todt et al., 2017).

A perimodiolar placement with the electrode contacts in close proximity to the spiral ganglion cells has been suggested as one of the factors contributing to the surprisingly good word recognition even after partial or subtotal cochleoectomy for removal of intracochlear schwannoma and CI (Plontke et al., 2020, Wagner et al., 2020). Besides electrode array design, advancements in audio processors and speech coding strategies are believed to influence speech and music perception in CI users. Fine structure processing uses the fine structure of a signal to transmit pitch differentiation and temporal cues (Riss et al., 2008), which has been shown to be advantageous in difficult hearing situations such as speech recognition in noise (Vermeire et al., 2010) and listening to music (Riss et al., 2014).

Main articles published in this field:

- Stefan K. Plontke, Laura Fröhlich, **Sebastian Cozma**, Assen Koitschev, Katrin Reimann, Rainer Weiß. Gerrit Götze, Ingmar Seiwerth, Sabrina Kösling, Torsten Rahne. Hearing rehabilitation after subtotal cochleoectomy using a new, perimodiolar malleable cochlear implant electrode array: a preliminary report. *European Archives of Oto-Rhino-Laryngology.* 2020; https://doi.org/10.1007/s00405-020-06098-1. (IF=1,750).

Scientific contributions /Clinical implications:

- This research represents the first surgical experience and audiological outcome using a new, perimodiolar malleable cochlear implant electrode array for hearing rehabilitation after subtotal cochleoectomy for intralabyrinthine schwannoma.
- **The paper from 2020 has 2 citations in ISI Web of Science platform**

Aim of the research

The research includes a case series and describes the first experience with a new, perimodiolar malleable electrode in an implant type with known high MRI compatibility and fine structure coding. This customized cochlear implants were used for patients with intracochlear schwannomas after subtotal cochleoectomy.

Methods

Electrode design. Based on an existing cochlear implant (CI) model (Synchrony, MED-EL, Innsbruck, Austria), the existing FORM19 electrode array was modified by adding malleable property to be placed around the residual modiolus after tumor removal from the cochlea via subtotal cochleoectomy. Malleability of the electrode array was achieved by incorporating a wire with shape memory properties (wire length: 25 mm, wire diameter: 0.19 mm) within the silicone elastomer of the electrode array. The 12 platinum electrode contact pads for delivering the electrical stimulation were opened on one side of the array only and the shape memory wire was incorporated in the lateral side of the electrode array still within the silicone elastomer (Fig. I.2-5.1). The malleable Nitinol wire keeps its shape until 90 °C. Beyond this temperature, the wire will get back to its initial straight configuration. The CI with the malleable electrode array was custom-ordered from MED-EL as a custom-made device (CMD) under the regulations 93/42/ EEC, Medical Device Directive.

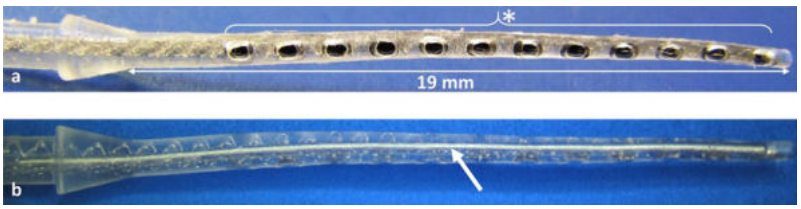


Fig. I.2-5.1. Design of the custom-made electrode array showing the 12 platinum electrode contact pads equally spaced at 1.3 mm intervals at one side (* in a) and the shape memory Nitinol wire on the lateral side of the electrode array (→ in b). The active stimulations range is 14.3 mm. The diameter at the basal end is 0.8 mm and the diameter at the apical end is 0.5 mm

MRI safety assessment by the manufacturer using comparative power deposition measurements using the 'Miniature Medical Implant Test System', revealed that this CMD electrode showed similar power deposition measurements as available standard electrodes under 0.2 T, 1.0 T, 1.5 T and 3 T MRI examination.

Patients. Between November 2018 and April 2019, the custom-made device (CMD) was implanted in four patients with intracochlear (1 ×), intravestibulocochlear (1 ×) and transmodiolar (2 ×) schwannomas (Figs. I.2-5.2, I.2-5.3 a, d and I.2-5.4 a, d). The four patients in this case series explicitly decided for this custom-made device combining the advantages of a high MRI compatibility and the possibility of a preformed perimodiolar electrode array.

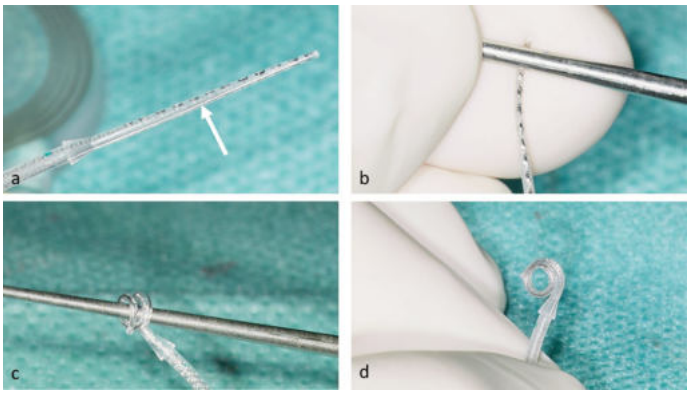


Fig. I.2-5.2. A new, perimodiolar malleable cochlear implant electrode array. The incorporated Nitinol wire (→ in a) allowed it to manually shape the electrode array by bending it around the shaft of a conical standard otological instrument like a Rosen needle (b–d)

Surgery. The surgical procedure for tumor removal through subtotal cochleoectomy and the cochlear defect closure has been described in detail elsewhere (Plontke, 2020, Plontke et al., 2020, 2018a, 2017). Since the electrode is preformed before placement, it cannot be inserted through the extended round window.

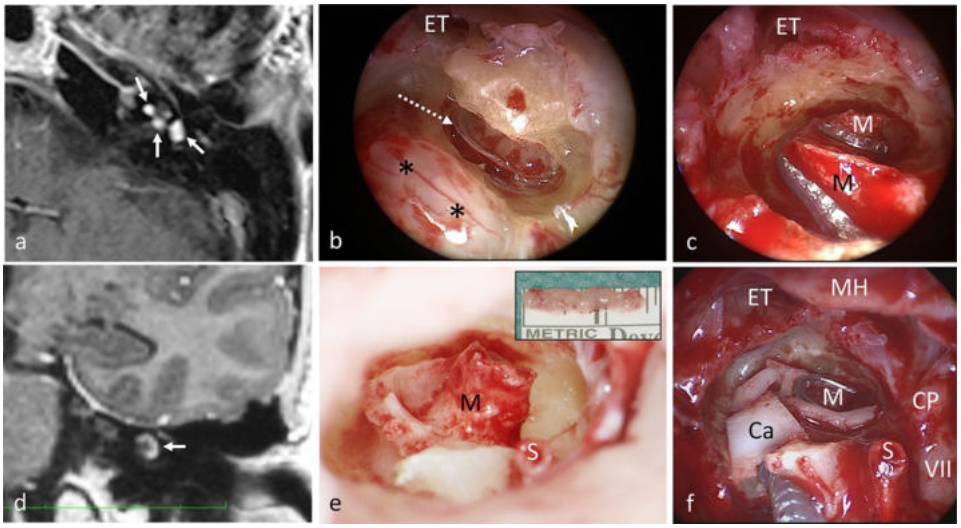


Fig. I.2-5.3. a MRI of pat. #1 (T1-w with contrast medium, axial) showing the tumor (→) in the cochlea, in the vestibule and in the fundus of the internal auditory canal. d MRI of pat. #2 (T1-w with contrast medium, coronal) demonstrating a solely intracochlear tumor (→) in a young patient. b, c, e, f Intraoperative views of patients #1 (b, c) and #2 (e, f). The intracochlear tumor parts of patient #1 can be seen in the basal turn (*) while the second turn is tumor free (b). The tumor from patient #2 is shown after removal in the insert in e. The perimodiolar formed electrode array was placed around the preserved basal and second turn modiolus (M). f Cartilage chips (Ca) were placed peripheral to the electrode array and the defect was closed with a cartilage-perichondrium-island transplant (not shown). Dotted arrow in b basilar membrane, VII facial nerve, CP cochleariform process, ET Eustachian tube orifice, MH Malleus handle, S stapes head, w weighted

The CMD electrode array was preformed before insertion by bending it manually with the finger tips and by the help of a "surgical claw" around the conical shaft of a standard otologic instrument (e.g., a Rosen needle) (Fig. I.2-5.2 b–d). Intraoperative microscopic and endoscopic images are shown in Figs. I.2-5.3 and I.2-5.4. If other surgical techniques for removing tumor from the cochlear scalae than partial or subtotal cochleoectomy are choosen (e.g., "push-through" or "pull-through"-techniques (Aschendorff et al., 2017, Plontke et al., 2018a) or if the electrode is to be inserted into the cochlea without tumor removal (i.e., by pushing a stiff array through the tumor (Carlson et al., 2016), this CMD electrode array cannot be used.

Outcome assessment. Outcome was assessed intraoperatively by impedance measurement as well as the recording of electrically evoked compound action potentials (ECAPs) and electrically evoked auditory brainstem responses (EABRs). Post- operatively, the feasibility of the surgical procedure was evaluated by measuring sound field thresholds to pulsed narrow band noise and word recognition thresholds for multisyllabic numbers and monosyllabic words in quiet at 65 dB SPL (WRS65) for the German speaking patients and with bisyllabic and monosyllabic Romanian words for one patient (patient #2) from Romania. Free field sound thresholds and word recognition were measured in quiet with exclusion of the contralateral ear by plugging and masking with white noise.

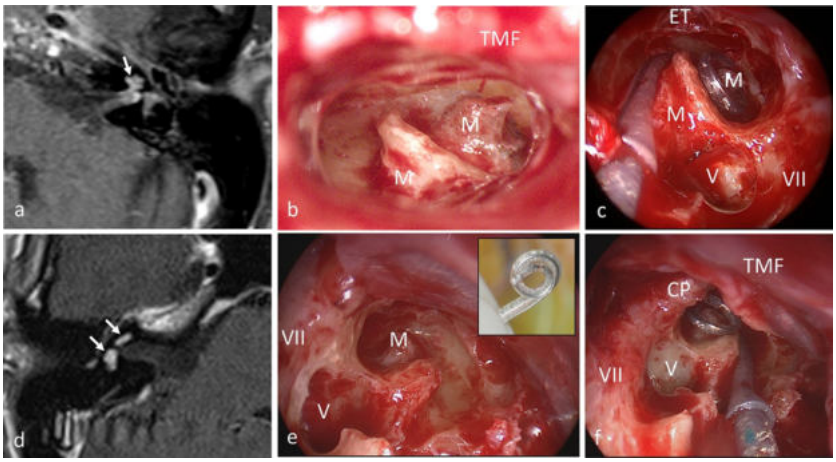


Fig. I.2-5.4. a MRI of pat. #3 (T1-w with contrast medium, axial) showing the tumor (→) in the basal and middle turn of the cochlea. d MRI of pat. #4 (T1-w with contrast medium, axial) demonstrating an intravestibulocochlear tumor (→). b, c, e, f Intraoperative views of patients #3 (b, c) and #4 (e, f). (M) modiolus, VII Facial nerve, CP cochleariform process, ET Eustachian tube orifice, TMF tympanomeatal flap, V vestibule, w weighted. Insert in e: perimodiolarly formed electrode array

Results

Surgical outcome. After tumor removal via subtotal cochleoectomy with or without labyrinthectomy, the new perimodiolar malleable electrode array could successfully be implanted in all four patients. Postoperative computed tomographys (CT) with the electrode arrays in their final position around the remaining parts of the modiolus are shown in Fig. I.2-5.5. **Audiological outcome.** Electrophysiological testing during surgery revealed normal impedances below 15 kΩ in all patients. The AutoART algorithm was able to detect ECAP thresholds for four electrodes in patient 1, two electrodes in patients 2 and 3 and one electrode in patient 4. In patients 2, 3, and 4, positive EABRs could be found for simultaneous stimulation of two apical, medial and basal electrodes, respectively. In patient 1, only one electrode was stimulated at a time and no positive EABR could be recorded (Fig. I.2-5.6). Six months after surgery, the free field pure tone thresholds in the four patients were 36, 28, 41, and 35 dB HL, and the WRS65 were 65, 80, 70, and 25% (one patient non-German speaking), (Fig. I.2-5.7).

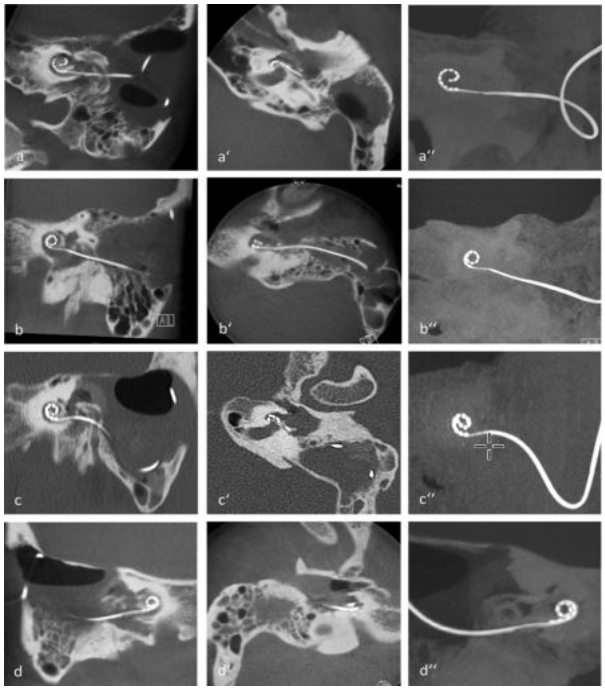


Fig. I.2-5.5. Postoperative Cone Beam Computed Tomography (CT) scans (apart from third row: high-resolution temporal bone CT) showing the electrode arrays in their final position with the remaining parts of the cochlea. a–d Paracoronal multi-planar reconstructions(MPR), a'–d' axial MPRs, a"–d" paracoronal maximum intensity projection (MIP), a–a" patient ID 1, b–b" patient ID 2, c–c" patient ID 3, d-d" patient ID 4

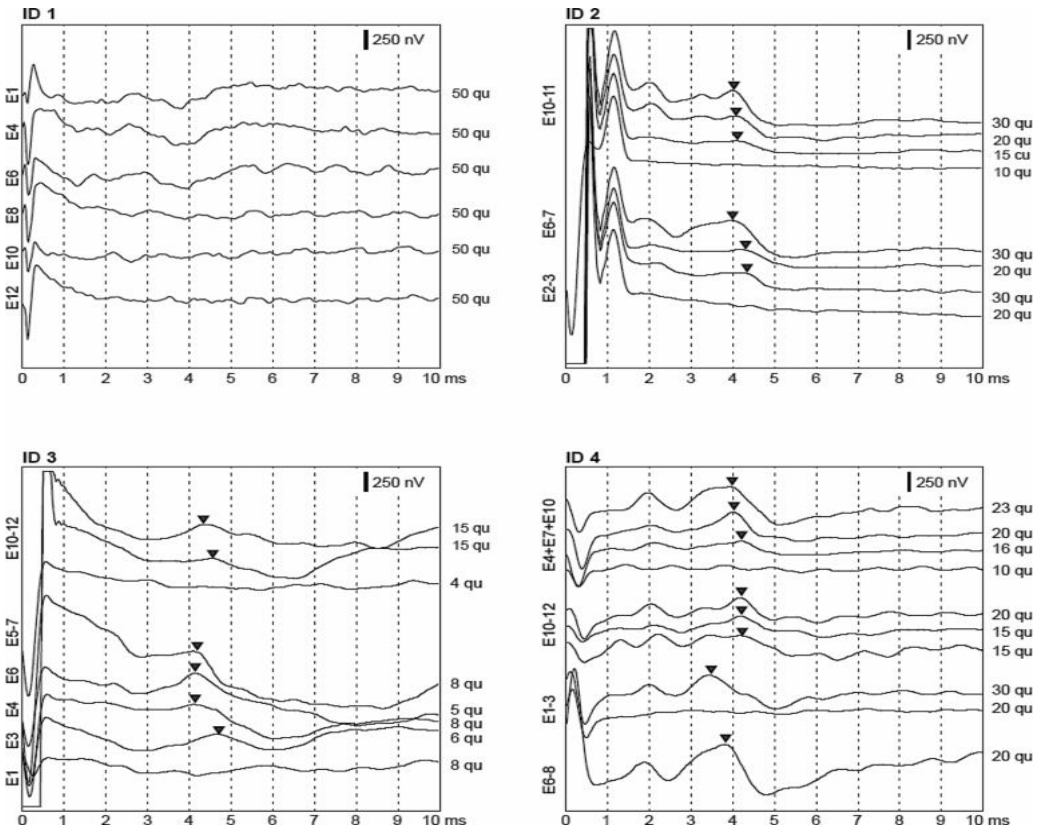


Fig. I.2-5.6. Electrically evoked auditory brainstem responses (EABRs) for all four patients. Stimulated electrodes are marked on the left, stimulation levels at the right sides of the subfigures. Triangles mark the wave V. No EABRs could be recorded in patient #1

Audio processor fitting and rehabilitation. Audio processor fitting could successfully be performed in all patients. Three patients are using a Sonnet audio processor, one patient is using a Rondo2 audio processor. Post-operatively, the impedances were higher compared to the intraoperative measurement but reached stable values below 15 kΩ after one week.

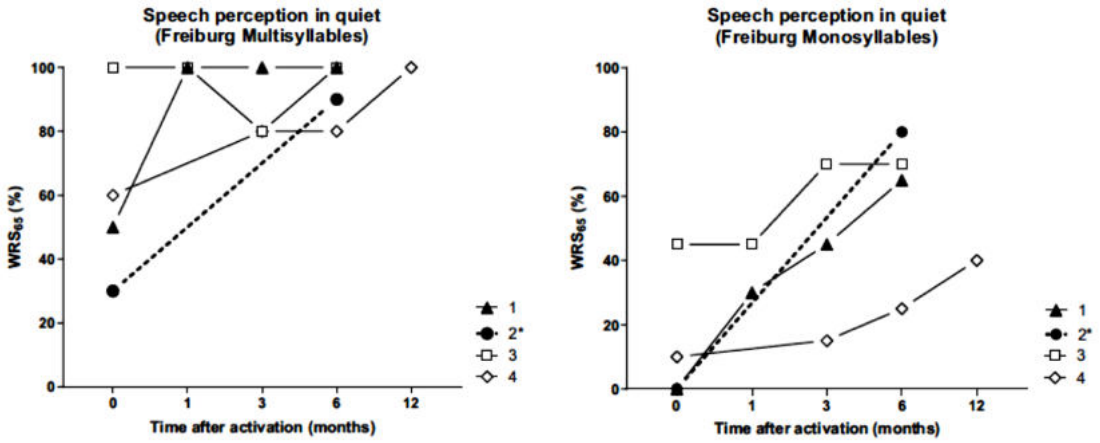


Fig. I.2-5.7. Word recognition score in quiet for multisyllabic numbers (left) and monosyllabic words (right), presented at 65 dB SPL (WRS65) as function of the time period after activation of the audio processor. *Romanian bisyllabic and monosyllabic words were used for this patient

Maximum comfortable levels (MCL) were found to be between 8.4 qu and 48.2 qu with higher stimulation levels in the apical region in patients 2, 3, and 4 compared to the basal MCL. In patients 2 and 3, the frequency allocation had to be altered based on the patients' tonotopy with channels 3 and 4 as the lowest frequencies. The most apical electrode 1 was allocated to the fifth frequency band (690–836 Hz) instead.

Discussion. The surgical evaluation demonstrated the feasibility of cochlear implantation with the new perimodiolar malleable electrode after subtotal cochleoectomy. Considering the substantial trauma through surgical tumor removal from the cochlea, and the long duration of deafness and tumor extensions in some of the patients, the audiological results showed good word recognition which was comparable to that observed with a standard perimodiolar electrode array (Plontke et al., 2020). Implant integrity could also be confirmed by electrophysiological testing during surgery. Impedances were normal and, while ECAPs were barely present, positive EABR could be elicited in three patients confirming the feasibility of the new electrode. While the recording of EABR in patient 1 was negative, this patient had the highest number of four electrodes with recordable ECAPs. It remains unclear, if the history of deafness for more than 20 years or the stimulation mode during EABR recording with only one electrode stimulated at a time were causing the absence of responses. However, despite the absence of intraoperative EABRs, the postoperative results in patient 1 showed good word recognition scores. All other patients had positive EABRs and showed a continuously increasing speech perception over time after audio processor fitting.

Compared to the previous experience with a preformed electrode array from a different manufacturer (Nucleus CI512, Cochlear ltd., Sydney, Australia) (Plontke et al., 2020, 2018a), the very tip of the electrode array could not be brought as close to the modiolus, since the wire does not reach to the very tip of the silicon carrier and bending at the very end was difficult. Electrophysiologically, this was also reflected by high stimulation levels needed for electrodes in the apical regions as shown in the patient's fitting maps and shorter battery life. In two patients, the frequency allocation had to be altered which was not necessary in all but one patient implanted with standard preformed electrode array (Plontke et al., 2020). Audio processor programming could successfully be performed in all patients without any adverse events.

There are alternative strategies to the subtotal cochleoectomy approach for tumor removal from the cochlea like a "double cochleostomy" with "pull-through" or "push-through" of the tumor (Aschendorff et al., 2017, Plontke et al., 2018a). This might result in incomplete tumor removal and increased risk for damaging the subtle structures of the modiolus through insufficient surgical overview. Some authors suggested cochlear implantation without tumor removal by pushing the electrode array through the tumor (Carlsonet al., 2016). However, due to tumor growth, e.g., from the cochlea to the vestibule with increasing symptoms like vertigo (Plontke et al., 2018b, Tieleman et al., 2008), this strategy seems only appropriate for selected cases. Our surgical technique with a subtotal cochleoectomy for tumor removal, with maximum approximation of the electrode contacts to the spiral ganglion cells in Rosenthal's canal, and peripheral cartilage placement (Plontke, 2020, Plontke et al., 2020, 2018a), is based on the hypothesis of a reduced spread of the electric field.

In the meantime, various manufacturers offer cochlear implants with "MRI-friendly", movable magnets in the receiver coil. Thus, the rationale behind choosing the manufacturer and the electrode type reported here, must be relativized.

In addition, in case of a necessary revision surgery, it is not possible to pull out the CMD electrode due to very high risk of "shearing off" the entire modiolus. To date, there is no published experience of revision surgery in cases of intracochlear schwannomas and CI. However, using the technique as described earlier (Plontke, 2020, Plontke et al., 2020, 2018a), simple removal and re-insertion is unlikely after. In these cases, we speculate that the initial surgical procedure needs to be repeated with a possibly higher risk for damaging the modiolus.

Conclusion. Considering the substantial trauma through surgical tumor removal from the cochlea, the long duration of deafness and the advanced tumor extension in three of the four patients, the preliminary audiological outcomes for this new perimodiolar electrode array showed good results which were comparable to those observed with a standard perimodiolar electrode array, while the MRI-friendly magnet of the receiver coil allows easy imaging follow up.

I.2.5.2. Study of the performance of cochlear implantation in inner ear's malformation

Background. The medical evaluation and management of children with profound hearing loss (HL) with associated inner ear developmental malformations presents a significant challenge even for the most experienced ear surgeons and audiologists. In recent years, the number of cochlear implantations in children has increased worldwide, as well as cochlear implantation in congenital malformations. First results related to cochlear implantation in children with inner ear malformations have been appearing since 1988 and encouraging results have also been reported (Graham et al., 2000). The results are better with the technological developing of cochlear devices, nowadays existing different electrode options for malformed cochlea including the customized electrodes.

Inner ear malformations are found in 15% - 20% of patients with severe or profound sensorineural hearing loss (Foshi et al., 2012, Park et al., 2000). Congenital malformations of inner ear may be considered in two broad categories (Jackler, 2005):

a) malformation of membranous labyrinth (complete membranous labyrinth dysplasia, cochleosaccular dysplasia and cochlear basal turn dysplasia);

b) malformations of both the osseous and the membranous labyrinth (Foshi et al., 2012) - classification system developed by Jackleret et al. (Jackler et al., 1987) and Sennauroglu and Saatci (Sennaroglu, Saatci, 2002).

Recently, X-linked deafness has been recognized as a third type of incomplete partition (Sennaroglu et al., 2006): the interscalar septs are present, the modiolus is completely absent.

Main articles published in this field:

- **Sebastian Cozma**, Oana Manolache, Raluca Olariu, Cristian Mârțu, Luminița Rădulescu. Cochlear Implantation In A Child With Complex Bilateral Inner Ear And Cochleo-Vestibular Nerve Malformations. *Romanian Journal of Oral Rehabilitation* 2015; 7(1): 64-70.

Scientific contributions /Clinical implications:

- Rare malformative cases raise important issues of clinical decision and surgical and audiological management. Similar cases similar to the presented one are very rare and involve a special complexity. Their responsible approach is a proof of clinical maturity and consolidation of professional experience.

Introduction

We present a complex case of a 8,6 years old girl, without family antecedents of deafness, full-term born without any neonatal intercurrence, not submitted to newborn hearing screening, who addressed to us for bilateral prelingually hearing loss. The patient was identified as having bilateral profound hearing loss and no language development at the age of 3 year old in another hospital. Immediately after, she was fitted bilaterally with conventional hearing aids without any benefit. Considering the new audiological reevaluation at the age of 8 years old and the child's previous evolution (absence of language acquisition) we decided that the only one possibility for the auditory rehabilitation is the cochlear implantation.

Material and methods

According to the age of the child, the audiological assessment was made either by subjective tests as pure tone audiometry (PTA) and free field audiometry without/ with hearing aids as well as objective tests: tympanometry and acoustic reflex, otoacoustic emissions, auditory brainstem responses (ABR) and auditory steady state responses (ASSR). All audiological tests were performed on calibrated Interacoustics equipment in soundproof rooms. The PTA revealed a profound hearing loss with residual hearing only at low frequencies on the right side and the free field audiometry with hearing aids showed a very poor gain. No auditory brainstem response could be evoked in any ear at a stimulation level of 100dB normal hearing level (nHL), otoacoustic emissions were absent bilaterally. No auditory steady-state responses were identified. Tympanometry was normal and acoustic reflex was bilaterally absent. We therefore decided to carry out cochlear implantation. Preoperative CT scan revealed a bilateral congenital inner ear malformation (cochlear common cavity deformity on the right side, cochlear aplasia on the left ear and bilateral vestibular malformation) (fig. I.2-5.8). Cerebral magnetic resonance showed the presence of some very thin nerve fibers corresponding to the single cavity of the inner ear on the right side, which seems to be just a branch of the vestibular right nerve (fig. I.2-5.9).

The child was submitted to right ear cochlear implantation procedure at 8,6 years old. The electrode-array was fully inserted through the cochleostomy. We verified the position of the cochlear implant's electrode array in the single cavity of the malformed right inner ear by post-surgery skull X-ray with two incidences (antero-posterior and lateral), which shown the portelectrode placed circularly near the common cavity wall, without any contacts between electrodes. The cochlear implant activation was performed one month after the implantation, when the patient had her first subjective sound perceptions.

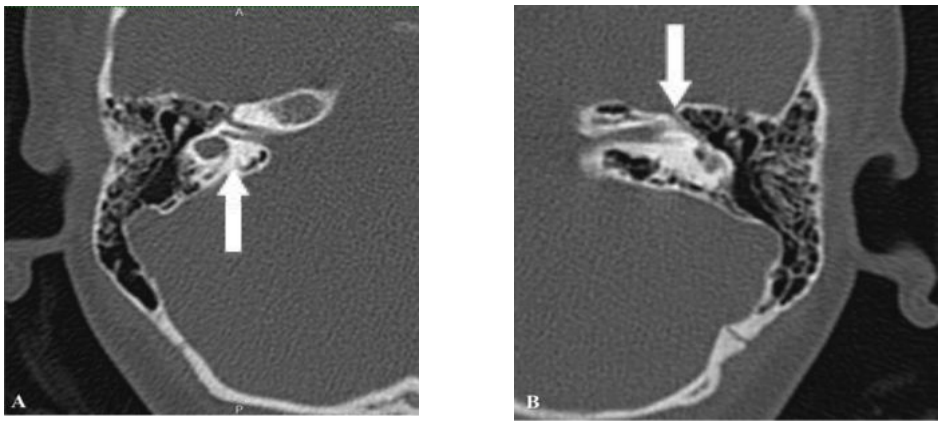


Fig. I.2-5.8. Preoperative CT scan of the temporal bone (axial plane)
A. Right ear: cochlear common cavity and vestibule malformation;
B. Left ear: cochlear aplasia and vestibule malformation.

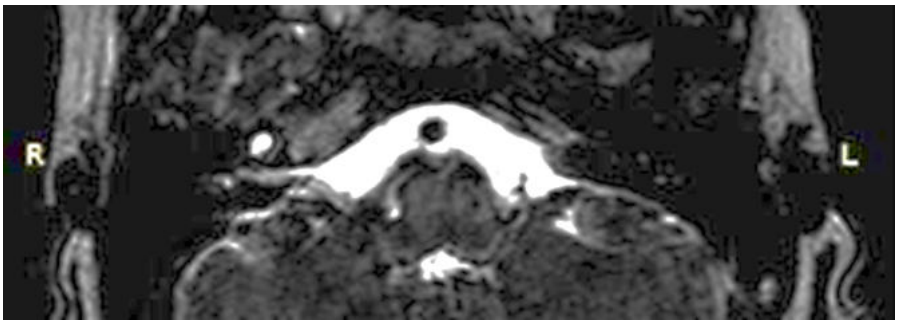


Fig. I.2-5.9. Preoperative MRI - very thin nerve fibers corresponding to the single cavity of the inner ear on the right side (branch of the vestibular right nerve)

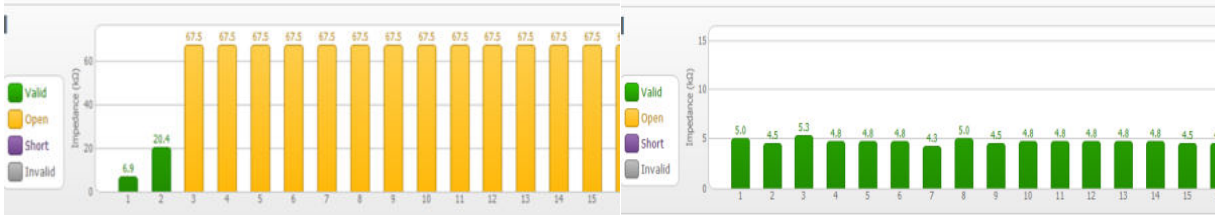
Postimplantation tonal auditory performance was measured using free field pure tone thresholds audiometry (PTA) in soundproof room. After the activation of the implant the patient was submitted to intensive speech therapy. We analysed the specialist reports and the family questionnaires to evaluate the speech performance by categories of auditory performance index (CAP) described by Archbold S. (2) and by speech intelligibility rating scale (SIR) (Samar, Metz, 1988).

Results

Telemetric results. High impedances were observed intraoperatively, as indication of open circuits for 14 of 16 electrodes. At the activation time we found normal values of impedances for all electrodes (fig. I.2-5.10). In terms of cochlear malformations, intraoperative impedances value profile is different from the one we encounter in patients implanted with normal cochlea. We have to note also that we did not obtain electrically compound action potentials by neural response imaging software.

Audiologic results. The postoperative audiological performance for our patient was good; the average PTA threshold changed from 56,25 dB HL at first audiological evaluation (5 months postactivation) to 33,75 dB HL at 8 months. We noticed a small increase of PTA thresholds in the next year with an average of 36,25 dB HL at last evaluation (22 months postactivation). According to PTA evolution, the patient achived a maximum performance characterized by an index of 5 for categories of auditory performance (CAP): the patient understand common phrases without lipreading/ understands conversation without lipreading with a familiar talker; on the speech intelligibility rating scale (SIR) our patient was placed on

category 3 (connected speech is intelligible to a listener who concentrates and lipreads within a known context).



a. **b.**

Fig. I.2-5.10. Impedances values measured intraoperatively (a) and at the activation time (b)

Discussion

The common cavity has a frequency of around 16-25% of all ear malformations. In the 4th week of intrauterine life, development of inner ear stops (Jackler, 2005, Casselman et al., 2001, Ramos et al., 2005). Complete aplasia of the labyrinth and cochlear aplasia are very rare (1-3 % of all ear malformations), usually associated with other malformations that affect the temporal bone and results from interruption of otic development at the 3rd gestational week (Ramos et al., 2005). Previous studies about malformed inner ear, have documented some problems with surgical approach, cerebrospinal fluid gusher, electrode migration (fixation and stabilization of the electrodes), aberrant facial nerve. The type of malformation generally dictates the surgical approach for implantation. Ramos et al. (Ramos et al., 2003) classified inner ear malformations into three groups with respect to the surgical possibilities of implantation: (a) gross malformation constituting surgical contraindications; (b) major malformations with high risk surgery; (c) minor malformations - the surgical risks is lesser than in the previous group. With the exception of cochlear aplasia, labyrinthine aplasia and agenesis of cochlear nerve, all cochleovestibular malformations can be implanted. Major malformations include common cavity and severe hypoplasia are often associated with cerebrospinal fluid leakage, meningitis. Minor malformations are considered to be light hypoplasia, abnormalities of the aqueduct and abnormalities of the vestibule.

In our case, we had two different inner ear anomalies: cochlear aplasia on the left ear constituting a surgical contraindication for cochlear implantation and common cavity with vestibule malformation on the right ear which is an implantable type of anomaly and for this patient the only auditory rehabilitation possibility. There were no intraoperative surgical difficulties. The postoperative results are mainly related to the surgical placement of the electrode and residual neural nerve fibers (Sennaroglu, 2010). For our patient we had an intracavity placement of the electrode, close to the inner wall, so close to the vestibular nerve fibers. The results of cochlear implantation in cases with inner ear anomalies are generally good and appear to be related to the history of hearing loss, the degree of malformation and residual neural function (Sennaroglu, 2010).

Research on children with cochlear implants suggests that there is a "critical period" (a rather fixed time window of opportunity for change), a "sensitive period" and "age-related plasticity" (less abrupt transitions for the plasticity of the system) for the optimal auditory stimulation for normal hearing and speech development (Harrison et al., 2005). The central auditory pathways are maximally plastic for a period of about 3,5 - 4 years of life being the optimal time to implant a young congenitally deaf; the reduced plasticity of the central auditory system in congenitally deaf children implanted after 7 years is correlated with relatively poor development of speech and language skills (Harrison et al., 2005, Dorman et al, 2007). In terms of audiologic performance, children with inner ear malformations may perform very well. Children with common cavity tend to steadily and significantly improve their audiological

skills over time and this development may be highly individual (Bille et al., 2015, Buchman et al., 2004). The particularity of our case consist in association of a complex inner ear malformation with a late cochlear implantation after 7 years of age, due to different factors: no newborn hearing screening program at his birth time, wrong hearing loss diagnosis and inadequate auditory rehabilitation for a long period of time including the critical and sensitive period for auditory system plasticity, lack of etiological diagnosis with no imaging exploration. The postimplantation speech and language performance was good considering all these factors with poorer results than in no malformed implanted ears but with comparable postrehabilitation auditory skills reported in cases with common cavity cochlear implantation (Buchman et al., 2004).

Conclusion

Children with inner ear malformations can safely benefit of cochlear implantation, a successful way of rehabilitation although complications should be expected and auditory responses may be highly variable and relatively moderate.Cochlear implantation is a safe and effective treatment option in children with common cavity. The majority of children with common cavity derive significant audiological benefit from implantation. The imagistic evaluation by high resolution CT scan and magnetic resonance imaging play an important role in detection and treatment of deafness in inner ear malformations.

I.2.6. Research on the reliability of cochlear implants

Introduction

Cochlear implants (CIs) restore functional hearing in individuals with profound to severe sensorineural hearing loss. They consist of two main components: the external part (microphone, speech processor, transmitter coil, and batteries) and the implanted part (receiver electronics, magnet and electrode array). The internal components require surgical implantation: the electrode array is inserted into the cochlea and the receiver package is either fixed onto or partly embedded in the temporal bone. Cochlear implantees use their device for daily communication. Most wear their systems throughout the day. Obviously, implanted parts of the CI need to be reliable and remain functional for many years (ideally for the life-time of the patient). In recent years, partly due to increasing hearing screening in newborns, implantation of very young chil- dren has become more common (Leigh et al., 2011). This practice has effectively increased the expected lifespan of CIs.

Providing a safe implant on a long-term basis requires that (1) devices must be designed with biocompatible materials, (2) the sterilization process must be effective, (3) design and materials must minimize chronic mechanical tissue trauma and resist mechanical impact, and (4) levels of electrical charge produced by the implant should not exceed those that can be safely supported by human tissues (including neural tissue) without damage. The design and the materials of the implant play a key role in meeting the requirements mentioned above.

The average survival time of implanted CI components has not yet been established. Commercially available CIs have been in routine clinical use for about 20 years, and so the technology is relatively new. Manufacturers typically provide a 10 year warranty. Reliability may be reported in terms of average failure rate (FR, i.e., failed to implanted devices ratio). To evaluate the incidence of device failures over time, CI reliability is usually reported in terms of ”cumulative survival rate” (CSR), i.e., the proportion of devices still functioning normally after a given time period. This measure is commonly used for other implantable devices such as cardiac pacemakers (ISO_Standard, 2019). For CIs, the longest time-period CSR was reported after 12 and 20 years, depending on the manufacturer (Battmer et al., 2009). Survival rates after longer periods are not yet known.

Device failure is defined as when the device is not functioning inside the manufacturer's specification and/or there is no or just insufficient clinical benefit for the patient (European consensus, 2005). There also are situations when the device needs to be removed for medical/surgical reasons, such as infection or flap necrosis. Device failure is classified according to the guidelines of the 2005 Cochlear Implant Soft Failures Consensus Development Conference Statement into hard and soft failures (Balkany et al., 2005).

Main articles published in this field:

- Rădulescu L, **Cozma S**, Niemczyk C, Guevara N, Gahide I, Economides J, Lavieille JP, Meller R, Bébéar JP, Radafy E, Bordure P, Djennaoui D, Truy E. Multicenter evaluation of Neurelec Digisonic(®) SP cochlear implant reliability. *Eur Arch Otorhinolaryngol.* 2013; 270(4): 1507-12. (IF=1,608)
- Eugen Horatiu Stefanescu, Marioara Poenaru, Nicolae Constantin Balica, Anca Tudor, Andreea Marinescu, Madalina Georgescu, Luminita Radulescu, **Sebastian Cozma**, Violeta Necula, Marcel Cosgarea. Reliability of Med-El Cochlear Implants in children. The Romania Experience. *International Journal of Engineering Research and Application.* 2016; 6(7-2): 25-30. ISSN: 2248-9622

Scientific contributions /Clinical implications:

- The international multicenter research carried out through the study of Neurelec implants updated indispensable information for the use of these implants, reliability being an important indicator that reflects the quality of the devices and their lifespan. The paper was rewarded by UEFISCDI.
- We also contributed to a similar retrospective multicenter study in Romania, on MedEl implants used in children, the data being the first of its kind in our country.

A. International multicentric study about the Neurelec Digisonic® SP reliability

Background

Several studies have reported reliability in terms of FR and CSR for various CI devices provided by Cochlear Ltd (Sydney, Australia), Clarion-Advanced Bionics LLC (Valencia, CA, USA) and Med-El (Innsbruck, Austria) (Battmer et al., 2009, Brown et al., 2009, Maurer et al., 2005, Soli, Zheng, 2010, Battmer et al., 2007, Venail et al., 2008). Only FR on a limited number of mixed generations of MXM-Neurelec CIs (Vallauris, France) has been reported in three studies (Maurer et al., 2005, Battmer et al., 2007, Venail et al., 2008) that were not specifically looking at Neurelec data. Over the past 5 years, more and more centers are using Neurelec CIs, thus more comprehensive data regarding the reliability of this system are urgently needed.

The aim of this study was to assess CSR and average FR of the Digisonic® SP, the latest generation of CIs released by Neurelec in March 2006, in a large group of implanted adults and children over a time frame of 5 years.

Materials and methods

A multicenter retrospective case series was conducted in this study, independent of the manufacturer. A questionnaire recording details of implantations was sent by the authors to nine CI centers (five in France, one in Poland, one in Greece, one in Algeria, and one in Romania) chosen for using significant numbers of the Digisonic devices in children and adults. The

questionnaire recorded the following patient details: date of birth; dates of first implantation, explantation, and re-implantation (if applicable); reasons for explantation (medical or apparent device problem); cases lost to follow-up (with reasons and date of the last visit); data on explanted device, including serial numbers, date of manufacture, and technical report from manufacturer documenting test outcomes. Moreover, in case of re-implantation, centers were asked if outcomes were worse, equal, or better with the new device. The general method to measure reliability (device failure, survival time, specifications, and classification categories included in the device failure reports) was in accordance with the International Consensus Group for CI Reliability Reporting (Battmer et al., 2010). Consequently, for explantation following auditory symptoms, non-auditory symptoms, or loss of performance (i.e. "soft failure" cases (Balkany et al., 2005), if clinical benefit was observed after reimplantation, the device was considered failed regardless of the conclusion of technical analysis by the manufacturer. Consistent with reliability reporting, loss to follow-up was reported in a specific category. FR is the ratio between failed devices and total implanted devices. CSR was calculated in accordance with the methodology described in ISO standard 5841-2:2014 (ISO_Standard, 2019). CSR and FR were calculated for all patients, and then separately for the adults and children subgroups.

Results

Over the nine participating centers, 672 patients (362 children and 310 adults) were implanted with Digisonic® SP between March 2006 and March 2011 and all were included in the present study. Among these 672 patients, 4 (all adults) were lost to follow up and 15 explantations were noted. Explantations were performed due to device failures in six cases and medical reasons in nine cases. Table I.2-6.A. shows the causes for device failures according to the manufacturer's technical analysis and the duration of device use before the occurrence of failure. The causes for device failure included three cases of hermeticity failure (1 child and 2 adults; hermeticity compromised the external ceramic case), head trauma (1 child), electrode array malfunction (1 child; 3 electrodes not properly connected to internal stimulator), and one of unknown cause (1 adult; progressive drop in performance, clinical benefit observed after re-implantation with a new device). For this last case, technical analysis did not reveal any implant malfunction. Nine devices were explanted due to medical reasons (1.35 %). These included three cases of infection of the skin flap covering the receiver/stimulator and one case of cholesteatoma in the implanted ear. Three patients with ossified cochleae were explanted because they had no clinical benefit with the CI (all of them refused re- implantation). One patient was explanted because he had been diagnosed with Neurofibromatosis type 2 after implantation, and one patient was explanted following a loss of clinical benefit (no benefit observed after reimplantation with new device from the same manufacturer). In this last case, the technical report from the manufacturer showed that the device was functioning within specifications.

Table I.2-6.A. Number of device failures by failure mode and duration of device use (in months) before failure is indicated in brackets

	Hermeticity	Trauma	Electrode array	Electronic	Soft failure
Children (n = 362)	1 (5)	1 (14)	1 (48)	0	0
Adults (n = 310)	2 (8, 27)	0	0	0	1 (17)
Total (n = 672)	3	1	1	0	1

The overall FR was 0.89; 0.83 % for children (patients younger than 18 years), and 0.97 % for adults (Table I.2-6.B.)

Table I.2-6.B. Failure rates and cumulative survival rates for children, adults, and combined

	Failure rates (%)	Cumulative survival rates
Children (n = 362)	0.8	98.48
Adults (n = 306)*	1	98.57
Total (n = 668)*	0.9	98.51

* Less 4 adults that were lost to follow up

The overall CSR over a 5 year period was 98.51 % (Table I.2-6.B), with 98.48 % for children (Table I.2-6.B) only and 98.57 % for adults only (Table I.2-6.B).

Discussions

Device reliability. Most explantation procedures are carried out following device failure, even though manufacturer analysis does not always confirm a device out of specification (Chung et al., 2010). Most device failures are spontaneous or due to head trauma (Battmer et al., 2009), but a small number (particularly ”soft” failures) involved breakage of electrode or receiver coil wires due to device/ electrode movement. Besides, duration of device use prior to failure did not show any specific pattern, as failures occurred 5–48 months after implantation. The failure modes observed in the present study appear to be consistent with other reports, though numbers were too small to obtain definitive rates for individual failure modes. Overall, device failure rates from previous studies are mostly in the 3–6 % range; however, as mentioned above, these reports cover a wide range of durations of CI use. A failure rate below 1 % was observed in the present study in a large cohort of Digisonic SP recipients at up to 5 years of device use.

In a previous study on CI failure on a very large number of implanted CIs (Battmer et al., 2007), mixing all CI generations for each manufacturer (including old generations of CIs) on a long time-span (since beginning of CI programs), the FR for mixed generation of Neurelec devices was 3.2 % (17 cases out of 527), compared to 2 % for Cochlear CIs (617 out of 8,581), 7 % for Advanced Bionics CIs (123 out of 1,761), and 9 % for MedEl CIs (179 out of 1,987). In the present study, the overall FR for Digisonic SP was 6 cases out of 627 (0.97 %). This difference underlines that Neurelec CIs are still improving in terms of reliability.

In this cohort, a CSR of 98.51 % at 5 years was noted. This compares favourably with independently published reports on devices from other manufacturers. For example, it was reported a 5 year CSR of 90.2 % for the Advanced Bionics HiRes 90 K device (Battmer et al., 2009), and 99.6 and 97 % for the Cochlear CI24 device (Battmer et al., 2009, Venail et al., 2008). Such statistics are helpful for CI candidates considering which device to elect for. In this context, it is important that valid comparisons can be made, which can only be ensured by standardized reporting in accordance with the definitions provided by the International Consensus Group (Battmer et al., 2010).

The causes of device failures are of major interest, not least for the manufacturer to implement corrective measures if indicated. In the present study, three device failures were due to hermeticity breakdown. As with other ceramic encased devices (Battmer et al., 2009), the most important rate of the device failures for the Digisonic SP were due to the hermeticity leakage (3 cases out of 6). While this failure mode still shows a low rate of incidence, similar problems have been reported for devices from all the other major manufacturers using non-ceramic technology (Brown et al., 2009, Kane, Mann, 2007): for example, (Brown et al., 2009) reported that 31 % (9 out of 29) of device failure was due to hermeticity issues on a group of 806 patients with various CIs. One failure due to head trauma in a child was reported, but numbers were too low to indicate any differences between CSR in children and in adults.

The CSR of the last generation of implants from Neurelec cannot be compared to that of previous generations' because published data are not available.

Explantation for medical reasons. Many studies have reported on a wide range of complications after CI surgery. Reports distinguished between "minor" and "major" complications, the latter being usually related to issues that require explantation. Minor complications include problems that can be solved with revision surgery without explantation, or without surgery. For example, tinnitus, facial stimulation, and pain can sometimes be relieved by electrode deactivation (Venail et al., 2008). In the present study, only major complications were reported.

Revision surgery rates reported in the literature vary from 2.9 % (McJunkin, Jeyakumar, 2010) to 11.2 % (Venail et al., 2008), several factors might account for this range. One revision surgery rate reported specifically for Digisonic SP CI users was 2.4 % (Guevara et al., 2010). A source of variability is the duration of follow-up for studied cohort. Longer duration will inevitably result in a higher total number of complications, in particular device failure. Even some recent reports include subjects who were implanted before 1990 (Chung et al., 2010, Cote et al., 2007), it is possible that prevalence of some failure modes may have changed over time.

Medical complications resulted in nine explantations in the present study (1.35 %), the most common of which was 'flap problems'. Flap-related problems are reported to be the most common major complication after device failure, and appeared to occur in about 1 % of cases in a previous study (Cullen et al., 2008). Strategies are proposed to avoid explantation in infected patients, considering primary immunodeficiency (Yu et al., 2001), but the most important factor appears to be the degree of vascular disruption caused by the surgery. This is clearly evidenced by all studies that have assessed minimal access surgery, for which less flap complications were reported (Cullen et al., 2008, Ray et al., 2004). The present study also included three cases with significant pre-operative ossification, which were eventually explanted due to limited clinical benefit. Strictly speaking, these do not represent either device failures or medical complications, and if these were excluded from statistics then the incidence of explantation due to medical complications would drop from 1.35 to 0.9 %.

Reliability reporting. There are multiple factors reflected in the CSR number. These include patient characteristics (age, malformations of the cochlea, ossification of the inner ear, etc.), features of the implanted device, surgical technique, and surgical skill. Taking these individuals and often interconnected factors apart is not possible.

The same standards and factors have to be followed by all studies reporting device reliability, thus making the results comparable to guide patients, clinicians, CI centers, and manufacturers. To be truly useful, a study regarding CI reliability would require:

– Conformance with International Consensus Group guidelines (Battmer et al., 2010, Balkany et al., 2005).

– The reliability measure has to be quantified with common methods—CSR and FR in the present study.

– Each and every CI model has to be assessed separately to compare reliability between them.

– The duration of device use must be long enough to be consistent in assessing the device FR. Counter-intuitively, a previous study has shown that 24 % of reimplantations due to device failure or infections occurred before 2.5 years and 72 % of them before the fifth year of implantation, suggesting that the longer the follow-up time, the smaller the number of reimplantations (Venail et al., 2008).

– Device failure data has to be systematically reported by all CI centers.

– Device failure assessment has to be conducted on a large number of implants. As observed by Battmer et al. (Battmer et al., 2009) the size of the studied cohort varies extremely from one study to another, influencing statistical robustness—smaller samples creating the

greater uncertainties. In addition, multicenter studies should be employed when a specific model of device is assessed to avoid any peculiarities linked to an individual center.

– The centers participating in studies must be choosen randomly. Cochlear implantation is performed by otologists with widely ranging skill levels and the study must give a reasonable impression regarding device reliability even in the hands of less experienced surgeons. The relation between FR and surgical skills was already emphazised in medical literature.

B. Study about the reliability of Med-El cochlear implants in children in Romania

Aim of the research

This study assessed the reliability of Med-El devices in children throughout Romania. This is a multicenter retrospective study based on a questionnaire which was completed by teams from 4 major CI centers requesting information about patients implanted with Med-El devices. Failure Rate (FR) and Cumulative Survival Rate (CSR) over a 5 year period were calculated for this group.

Materials and methods

In 2001 Romania started a National Program for Cochlear Implantation, and since then 256 children received different types of Med-El devices in the four major Romanian Cochlear Implant Centers (Bucuresti, Iasi, Cluj, and Timisoara). Written Informed Consent was obtained from parents when entering the Romanian National Cochlear Implant Program.

A retrospective review of the cochlear implant database and the medical records of implanted patients were performed: total number of patients implanted with Med-El devices, patients for each type of device, demographic data, age at implantation, cause of deafness, malformations, and complications. The median (SD) age at initial implantation was 49 (23) months. A 60 month follow up period was mandatory for including in the study.

We designed a questionnaire to assess the incidence, the time elapsed and the mode of device failure and we sent it to the other three major cochlear implant centers in Romania. We also collected information on reasons for reimplantation and data on explanted devices (serial numbers and manufacturer's technical report) as shown in Table I.2-6.C.

Total nr of children implanted with Med-El devices, - Nr of cases / type of device, - follow up period for each patient (Months)	- Date of first implantation MM/YYYY - Type of Med-El Device -Intraoperative complications: Yes/No -Specify	- Date of device failure, explantation/ re-implantation MM/YYYY - Type of re-implanted Device - Reason for explantation - Problems at explantation/ reimplantation Specify	-Type of explanted device -Manufacturer raport - Cause of failure - serial number - other - specify	Speech perception evaluation after reimplantation -improving - same - deteriorating

Table I.2-6.C. Questionnaire

The MedEl devices used for implantation were: Combi 40+, Pulsar and Sonata. All explanted children were reimplanted using Med-El devices. Data regarding the patients requiring reimplantation are shown in Table I.2-6.D.

In all four centers cochlear implantation was performed using the classic technique with mastoidectomy and posterior tympanotomy. The insertion of the electrode was performed either through a cochleostomy or through the round window. In all cases it was used a double flap technique with either a large or a small incision (performed in only one center). The fixation of the device with intraosseous sutures was performed in all but 32 cases operated in one center, on very small children with a very thin skull using the small incision technique. In such cases the periosteal pocket technique as described by Adunka and Buchmann was used even for ceramic devices.

Children requiring reimplantation	17	
Male	10	59%
Prelingual onset of hearing loss	16	94%
Age at implantation, median/range, mo	49	12-156
Time to reimplantation, median/range, mo	22	5-54
Same side reimplanted	14	82%
Complications at first implantation	2	12%
Same model reimplanted	13	76%
Cause of deafness		
Congenital; unknown	13	76%
Congenital; genetic	3	18%
Other (CMV infection)	1	6%

Table I.2-6.D. Reimplanted children

The policy of reimplantation consists of using the ipsilateral side whenever possible and to preserve the opposite ear. In case of flap necrosis that could not be reconstructed or active infection that was nonresponsive to treatment, the device was removed leaving the electrode in the cochlea to prevent cochlear obstruction. The same ear was reimplanted later on. If not possible, the opposite side was considered. The FR and the CSR of the Med-El devices were calculated in accordance with the new consensus statement proposed by International Consensus Group for CI Reliability Reporting.

Results

There were 256 patients included in this study. The Cumulative Survival Rate (95.31%) and Failure Rate (6.64%) at 5 years were calculated (Figs. I.2-6.1 and I.2-6.2).

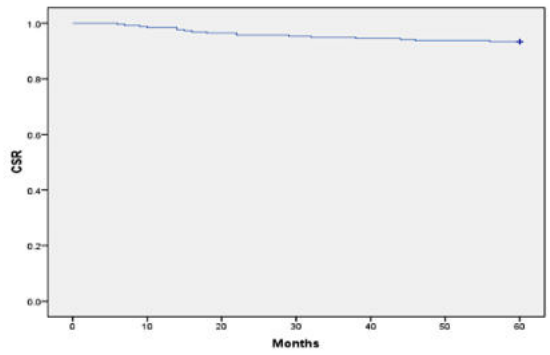


Fig. I.2-6.1. Cumulative Survival Rate at 5 Years. Overall rate – 95.31%

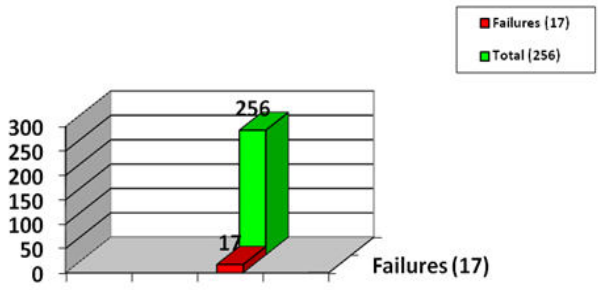


Fig. I.2-6.2. Failure Rate of Med – El Devices. Failed- red; implanted devices-green

There were no significant differences between the four centers regarding the CSR at 5 years (Mantel-Cox log-rank test, p=0.541, significant level α=0.05) but the number of cases was significantly different and the total number of cases is quite small (Fig. I.2-6.3).

None of the cases was lost to follow-up. There were seventeen (6,64%) cochlear re-implantations in this group with a mean duration of usage before failure of 22 months (range 5–54 months). This was especially the case with Pulsar devices. The number of Pulsar devices that failed exceeded by far the other types of Med-El devices (Fig I.2-6.4).

There were 12 device failures and another 5 cases that required re-implantation due to medical/surgical reasons so, in all, 17 devices had to be replaced by the end of the 60 month follow-up period (Fig. I.2-6.5).

Flap-related problems were the main medical/surgical reason for re-implantation.

There was only one case of posttraumatic device failure. We did not find any correlation between meningitis and device failure as none of the children requiring revision surgery had meningitis as cause of deafness.

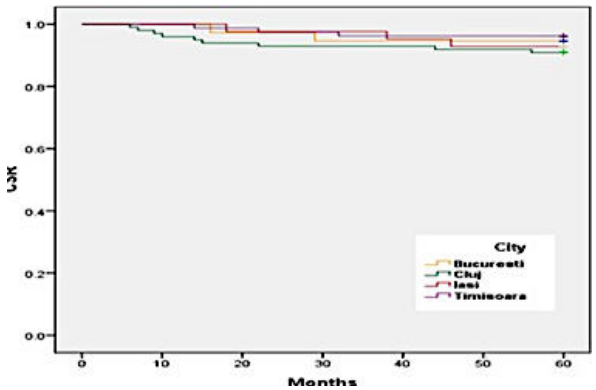


Fig. I.2-6.3. Cumulative Survival Rates in the four Centers. Yellow-Bucharest; Green-Cluj; Red-Iasi; Purple-Timisoara

The type of failure for seven of the devices in the present study was described by the manufacturer as a hermiticity failure. One implant failed secondary to a problem to the ground electrode. In four patients, no clear reason for failure has been found.Four patients requiring re-implantation received a different device model (23%).

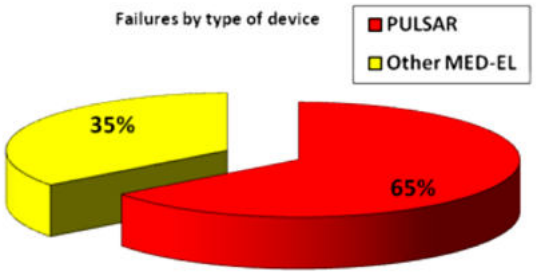


Fig. I.2-6.4. Med-El failures by device type. Pulsar devices-red; Other types-yellow

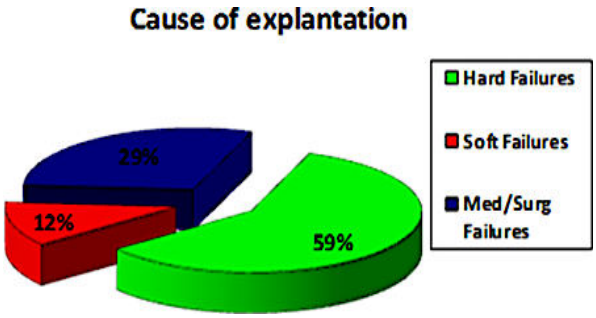


Fig. I.2-6.5. Cause of explantation. Hard Failures-green; Soft Failures-red; Medical/Surgical Failures- blue

Discussions

The reimplantation rate in children in the literature ranges from 4% to 15.4% (Marlowe et al., 2010, Cullen et al., 2008, Gosepath et al., 2009, Fayad et al., 2006, Lassig et al., 2005), so our rate (6.64%) is closer to the better end but there was a very short duration of usage before re-implantation: 22 months.

Surgical Technique. The intraosseous suture fixation of the implant was used in all but 32 cases where the fixation of the ceramic device was performed by using the periostal pocket technique as described by Adunka and Buchmann (Adunka, Buchman et al., 2007). In this group there was only one case that required reimplantation and the reason was a progressive decrement in performance of the device (soft failure). The failure rate in this group was 3.12% but the group was too small to come to any conclusion. Alexander et al (Alexander et al., 2011) saw no association between non suture fixation methods they used and failure rate in a series of 320 devices monitored for a median of 26 months.

In our series re-implantations were performed due to medical/surgical reasons in 5 cases: 3 cases of infection/ necrosis of the skin flap and 2 cases of chronic infection/

cholesteatoma in the implanted ear. Flap-related problems are reported to be the most common complication after cochlear implantation. The cause of flap related problems seems to be the degree of vascular disruption caused by the surgery. This is supported by all studies that have assessed minimal invasive surgery, for which less flap complications were reported (Cullen et al., 2008, Ray et al., 2004). In our study more than half of the devices had ceramic housing and a large incision was used (except for the 32 cases already discussed and for the non ceramic ones).

Revision surgery implies at least the same risks and complications as the first operation. As we do not know how many times we need/can successfully replace the electrode array, the insertion of the electrode should be as gentle as possible and every surgery as atraumatic as possible (Eskander et al., 2011).

Etiology of Deafness. In our series none of the patients requiring CI reimplantation had bacterial meningitis as the cause of hearing loss. Overall meningitis as an etiologic factor accounts for 6% of all patients in our group.

Type of Device. In our series of Med-El device users, we assessed the survival rate of different device generations from the same manufacturer. We found that, at this time, the Combi 40+ shows the best survival and the smallest failure rate. The Pulsar has the worst results and also the shortest time to failure. For Sonata devices we do not have a significant number of cases that completed the 60 month follow up period when comparing to Pulsar and Combi 40+.

Cause of Device Failure. Most revision surgeries were performed following device failure, though manufacturer's report does not always confirm a certain cause for this. Most device failures are spontaneous (Battmer et al., 2009). The time elapsed to failure did not show any specific pattern, as failures occurred 5–54 months after implantation. Hermiticity problems seemed to be much more frequent – 7 out of 12 devices (58%) and were encountered mostly in ceramic devices. This issue was also observed in other studies - Brown et al. (Brown et al., 2009) reported that 31 % (9 out of 29) of device failure was due to hermiticity issues in a group of 806 patients with various types of cochlear implants.

The results in our study compares favorably with other published reports on device failures from other manufacturers. Failure Rate for Neurelec devices was 3.2 % (17/527), 2 % for Cochlear (617/8,581), 7 % for Advanced Bionics (123/1,761), and 9 % for Med-El (179 /1,987) (Battmer et al., 2007).

Conclusions

Cochlear implant revision surgery is an increasing part of the surgical activity in a cochlear implant center. Cochlear implant reliability data should be considered during the choice of an implant for each individual patient.

In order to allow comparison between different CI system's reliability studies, it is crucial to keep the rules for device failures reporting and for CSR calculation unchanged in the future.

A. The FR and the CSR of the Digisonic SP were calculated in accordance with the new consensus statement designed by International Consensus Group for CI Reliability Reporting. The FR was better when compared to previous generation of Neurelec CIs, and was comparable to FR from other manufacturers. CSR was found to be comparable or better, in specific cases, to that of other CIs available on the market.

B. The Med-El cochlear implants have proven to be excellent devices for children with profound hearing loss. CSR was found to be comparable to that of other cochlear implants (from different manufacturers) available on the market.

Other articles published in this field:

- D. Mârţu, Luminiţa Rădulescu, **S. Cozma**, A. I. Curcă. 7 ani de implant cohlear în Clinica ORL a Spitalului Clinic de Recuperare Iaşi. (7 years of cochlear implant in the ENT Clinic of the Iaşi Rehabilitation Clinical Hospital). *The Medical-Surgical Journal.* 2008; 112 (1): 130-135. ISSN 0048-7848
- D. Mârţu, Luminiţa Rădulescu**, S. Cozma,** Rodica Prodan. Primul implant cohlear binaural efectuat în România. (The first binaural cochlear implant performed in Romania). *The Medical-Surgical Journal.* 2008; 112 (2-s.2): 186-189, ISSN 0048-7848
- Luminiţa Rădulescu, C. Mârţu, D. Mârţu, G. Damean, B. Cavaleriu, **S. Cozma**. Reimplantarea cochleară la copil – cauze, dificultăţi şi rezultate. (Cochlear reimplantation in children - causes, difficulties and results). *The Medical-Surgical Journal.* 2015; (2-s.1): 82-86. ISSN: 0048 - 7848
- Luminița Rădulescu, Cristian Mârțu, Roxana Șerban, Corina Butnaru, Alexandra Doroftei, **Sebastian Cozma**. Calitatea vieții la copilul mic cu implant cochlear. (Quality of life in young children with cochlear implants). *The Medical-Surgical Journal.* 2017; 2(s.1): 12-19. ISSN: 0048 - 7848
- Dan Mârţu, Luminiţa Rădulescu, **Sebastian Cozma**, Aurelian Curcă. Indicaţiile implantului cohlear. (Indications of cochlear implantation). *The Medical-Surgical Journal.* 2007, 111 (4-s.1): 7–10. ISSN 0048-7848
- D. Mârţu, **S. Cozma**, Luminiţa Rădulescu, C. Mârţu. Tratamentul modern al hipoacuziei neuro-senzoriale. (Modern treatment of neuro-sensory hearing loss). *Supliment al Revistei de Medicină Stomatologică.* 2003, 7(4): 332–337. ISSN 1453-1224.
- D. Mârţu, Luminiţa Rădulescu, **S. Cozma**, Annabella Vizitiu. Indicaţii limita ale implantării cochleare. (Limit indications of cochlear implantation). *Supliment al Revistei de Medicină Stomatologică.* 2002; 6(1): 251-264, ISSN 1453-1224
- **S. Cozma**, Simona Şerban, D. Mârţu. Managementul audiologic al pacientului cu implant cohlear. (Audiological management of the patient with cochlear implant). *The Medical-Surgical Journal.* 2007; 111(1- s.2): 327-331, ISSN 0048-7848
- Marius Cristian Martu, **Sebastian Cozma**, Vasile Dan Martu, Roxana Serban, Dragos Bularda, Corina Butnaru, Mihaela Luminita Radulescu. Cochlear Implant Strategies and Biomaterials from Past to Future. *Materiale Plastice.* 2017; 54(4): 788–794; (IF=0,838).

I.3. RESEARCH REGARDING THE VESTIBULAR FUNCTION, THE DIAGNOSTIC AND TREATMENT IN BALANCE DISORDERS

I.3.1. Subjective and objective diagnostic instruments in vestibular disorders

Background

After headache, vertigo and dizziness are among the most frequent presenting symptoms in ENT, in neurology and internal medicine clinics. A survey of over 30,000 persons showed that the prevalence of vertigo lies around 17% and rises up to 39% in those over 80 years of age (Davis, Moorjani, 2003). Vertigo and dizziness are not a unique disease entity. The terms cover a number of multisensory and sensoriomotor syndromes of various aetiologies and pathogenesis, which can be elucidated only on an interdisciplinary approach. Combined visual, somatosensory and vestibular inputs are required in order to maintain the body balance. Any dysfunction in one of these channels may lead to vertigo and imbalance (Nasher, 1997). A common perspective of ENT doctors, neurologists, and general medicine physicians is needed for a better diagnosis and treatment of vertigo and dizziness patients. Whether caused by physiological stimulation (motion sickness, height vertigo) or a lesion (unilateral labyrinthine failure, central vestibular pathways lesions), the resulting vertigo syndrome characteristically exhibits similar signs and symptoms, despite the different pathomecanisms – dizziness/vertigo, nausea, nystagmus, falling tendency/ataxia (Brandt et al., 2005).

VEMP (vestibular evoked myogenic potentials) is a test that is part of the protocol for evaluating peripheral vestibulopathy objectifying the saccular activity (cervical VEMP) and utricle activity (ocular VEMP), sensors for linear accelerations. These potentials are based on a multineuronal reflex and record the vestibular activity evoked by sound stimuli expressed at the muscular level (sternocleidomastoid muscle for cervical VEMP and periocular muscles for ocular VEMP). Objectification of the saccular and utricular function deficit by VEMP offers the possibility of a correct treatment and the exclusion of other differential diagnosis.

Main articles published in this field:

- Adina Roceanu, Dafin F Muresanu, Bogdan O Popescu, Daniela Anghel, Madalina Georgescu, **Sebastian Cozma**, Luigi Marceanu, Silviu Albu, Ovidiu Bajenaru. Taking History For Vertigo And Dizziness–A Practical Approach. *Romanian Journal of Neurology.* 2014; 13(3): 108. ISSN: 1843-8148
- **S. Cozma**, Cristina Hera, Oana Bitere, C. Mârțu, Luminița Rădulescu. Rolul VEMP în explorarea pacientului cu tulburări de echilibru - experiența noastră. (The role of VEMP in exploring the patient with balance disorders - our experience). *The Medical-Surgical Journal.* 2017; 2(s.1): 20-27. ISSN: 0048 - 7848
- **S. Cozma**, Cristina Hera, Oana Bitere, C. Mârțu, Corina Dima-Cozma, Luminița Rădulescu. Rolul posturografiei dinamice computerizate în evaluarea și tratamentul vestibulopatiilor bilaterale. (The role of dynamic computerized posturography in the evaluation and treatment of bilateral vestibulopathies). *The Medical-Surgical Journal.* 2016; 2(s.1): 32-42. ISSN: 0048 - 7848

Scientific contributions /Clinical implications:

- On behalf or Romanian Society of Neuro-Otology a **consensus** of specialist was reach in order to cover important issues in taking history of patient of vertigo and dizziness.
- A research branch analyzed the profile of the types of vestibular syndromes and quantified their incidence in patients who address for vertigo in the neurology and ENT departments
- A second research direction followed the contribution of modern objective diagnostic tools (cVEMP, oVEMP and computerized dynamic posturography) to the evaluation of patients with balance disorders for proper diagnosis and treatment.

Bilateral vestibular deficiency represents a real difficulty for the patients to perform daily activities. Sensory organization tests contribute to the diagnosis of the vestibular pathology, having an important role in distinguish the isolated vestibular input dysfunctions or those associated with other balance disorders generating deficits. Computerized dynamic posturography system is also an important instrument for balance rehabilitation by developing new strategies of posture control and accelerating vestibular compensation.

I.3.1.1. Research on anamnestic data in vertigo – essential element of vestibular diagnostic

The history of a patient with vertigo and dizzines must point out several characteristics: mode of onset, description of vertigo, associated signs, balance disturbances, history taken from witness of the attack (Table I.3-1.A).

I. The mode of onset of simptomatology:

– Abrupt onset – attacks of vertigo, or Slow, progressive onset of dizziness

II. Description of vertigo:

1. *clinical course*
   - Vertigo attacks (unique, multiple),
   - "continue" – dizziness
2. *the description of the sensation felt by the patient – the type of vertigo:*
   - Rotator like riding "merry-go-round (vestibular neuritis),
   - linear movement,
   - lateral deviation,
   - unsteadiness like in a "boat trip" (phobic postural vertigo),
   - numbness (drug intoxication)
3. *the duration of an attacks and the frequency of vertigo attacks;*
   - seconds – minutes – vestibular paroxysmia transient ischemic attacks;
   - hours – Menière disease, vestibular migraine, transient ischemic attacks;
   - days to weeks – vestibular neuritis
4. *factors that precipitates or exacerbates the vertigo attacks*
   - change in head position (VPPB – benign parox- ysmal positioning vertigo),
   - coughing, pressing, loud sounds "Tulio Phenomenon" (perilymph fistula)
   - physical activity, walking (bilateral vestibulopathy) changes in altitude, diving (barotraumas)
   - stress (psychogenic vertigo)
5. *the presence of clinical signs between vertigo attacks (neurological, cardiovascular)*

III. The presence of signs associated to vertigo

1. *auditory signs – hypoacusis, tinnitus, fullness in one ear, ear pain*
2. *neurological signs;*
   - cranial nerves – nystagmus, diplopia, strabismus, reduce hearing and reduced vision, trigeminal, facial nerve damage motor, sensitive, coordination pathways impair- ment
   - other neurological signs – headache, loss of consciousness, autonomic nervous signs

IV. Patient history related to balance disturbance

1. *history of cerebral trauma*

2. *ENT diseases*
3. *neurological disease*
4. *cardiovascular, metabolic, haematological diseases*
5. *local or general medications (amino glycosides, sedatives, anti-hypertensive drugs)*
6. *neurosurgery or otic surgery*
7. *infectious disease (ear, cerebral, general)*
8. *psychiatric illnesses*
9. *professional risk factors*
10. *genetic, familial diseases*

V. History taken from the witness of vertigo attacks

1. *the presence of nystagmus*
2. *falling*
3. *loss of consciousness*

Table I.3-1.A. History of a patient with vertigo and dizziness

The real vertigo is described as illusion of motion of the environment and of the patient's body. Also, patients describe "to-and-fro" and "up-and down" sensation". The subjective vertigo is the sensation of turning one's body around the environment. The objective vertigo is the illusion of environment motion around the patient. Vertigo can be paroxysmal, permanent, transient or positional. **Pseudovertigo** – dizziness, giddiness – must be distinguished by the real vertigo – than patient com- plaints of light-headedness, felling of swaying, im- balance – but without objective neurological or ENT signs (Ropper, Brown, 2005). According to the cause of vertigo and dizziness, in clinical practice we can identify: non-vestibular vertigo and vestibular vertigo. **Non-vestibular vertigo** could be due to ortostatic hypotension, anaemic syndrome, cardiac arrhytmias, drug intoxication, hypoglycaemia, phobic vertigo, but also neurological causes (epilepsy, acute oftalmoplegia, paraneoplastic syndrome, cerebellar ischemia, basilar migraine) (Table I.3-1.B).

1. *orthostatic hypotension*
   - primary
   - due to over – treatment of arterial hypertension
   - due to neurological causes (adverse event in levodopa therapy in Parkinson disease, sensitive polyneuropathy with impairment of proprioceptive and vibratory sense in diabetes, nerosyphilis)
2. *anaemic syndrome*
3. *cardiac arrhythmias*
4. *drug intoxication with sedative, barbiturics*
5. *hypoglycaemia*
6. *anxiety and panic attacks, phobic vertigo*
7. *neurological causes of non-vestibular vertigo*
   - • epilepsy
     - focal vestibular epilepsy–vertiginous sensation due excitation of superoposterior or the junction between parietal and temporal lobes
     - vestibulogenic epilepsy–reflex epilepsy due to vestibular stimulation
   - • acute oftalmoplegia
   - • paraneoplastic syndrome–opsoclonus
   - • ischemia in posterior-inferior cerebellar artery territory, flocullonodular lobe
   - • medullo-pontine lesions–of nucleus prepositus hipoglosii
   - • basilar migraine

Table I.3-1.B. Causes of non-vestibular vertigo

Vestibular vertigo could be due to labyrinthe lesions, acustico-vestibular nerve lesions, brainstem lesions, cerebellar lesions, familial vestibule-cerebellar syndrome (Table I.3-1.C).

1. labyrinthine lesions
- Menière disease
- Benign positional vertigo
- Vestibular neuronithitis
- Toxic and idiopathic bilateral vestibulopathy
- Toxic, infectious labirinthitis,
- Serous labirinthitis accompanying medium otitis
- Post-traumatic labirinthitis following withplash trauma, fracture of temporal bone
- Paroxysmal vertigo of childhood
- Cogan syndrome (nonsyphilitic interstitial keratitis with vertigo, tinnitus, nystagmus, rapidily pregressive deafness)

2. acustico-vestibular nerve lesions
- tumors of cerebello-potine angle
- acoustic neuroma (vesibular Schwannoma),
- neurinoma of trigeminal (gassserian) ganglion or neibhoring cranial nerves
- meningioma of cerebello- pontine angle
- cholesteatoma (epidermoid cyst)
- glomus jugulare tumor
- meningeal inflammations
- vascular compressions

3. brainstem lesions
- vascular – ischemic stroke in vertebro-basilar territory
- demyelinative lesions – in multiple seclerosis
- brainstem glioma

4. cerebellar lesions – vascular lesiuons (infarctions, hemorrhage)

5. familial vestibulo-cerebellar syndrome

Table I.3-1.C. Causes of vestibular vertigo

We developed an observational study in order to evaluate the most frequent causes of vertigo in clinical practice (Roceanu, Băjenaru, 2006). We evaluated 210 patients with vertigo, addressed to our dizziness unit (Roceanu, Băjenaru, 2006). We found different type of vertigo syndromes (Fig. I.3-1.1) with the following relative frequency: psychogenic vertigo (phobic postural vertigo, panic attacks, visual vertigo – "supermarket syndrome" – 27,61%; central vestibular vertigo after ischemic stroke – 18, 09%; chronic dizziness (multisystem sensory deficiency syndrome) – 13,80%; benign paroxysmal positioning vertigo – 13,80%; vestibular neuritis – 9,04%; Menière's disease – 5,23%; various other disorders (toxic vestibulopathy, vertiginous epilepsy, multiple sclerosis, acoustic neuroma, etc.) – 10,47%.

Disorders of the vestibular periphery cause nystagmus in a direction determined by the pattern of involved labyrinthine semicircular canal. The complete, unilateral loss of one labyrinth causes a mixed horizontal-torsional nystagmus that is suppressed by visual fixation. Loss of peripheral vestibular function causes impaired vision and oscillopsia during locomotion. Central vestibular disorders lead to upbeat, downbeat or torsional nystagmus (Hughes et al., 2006).

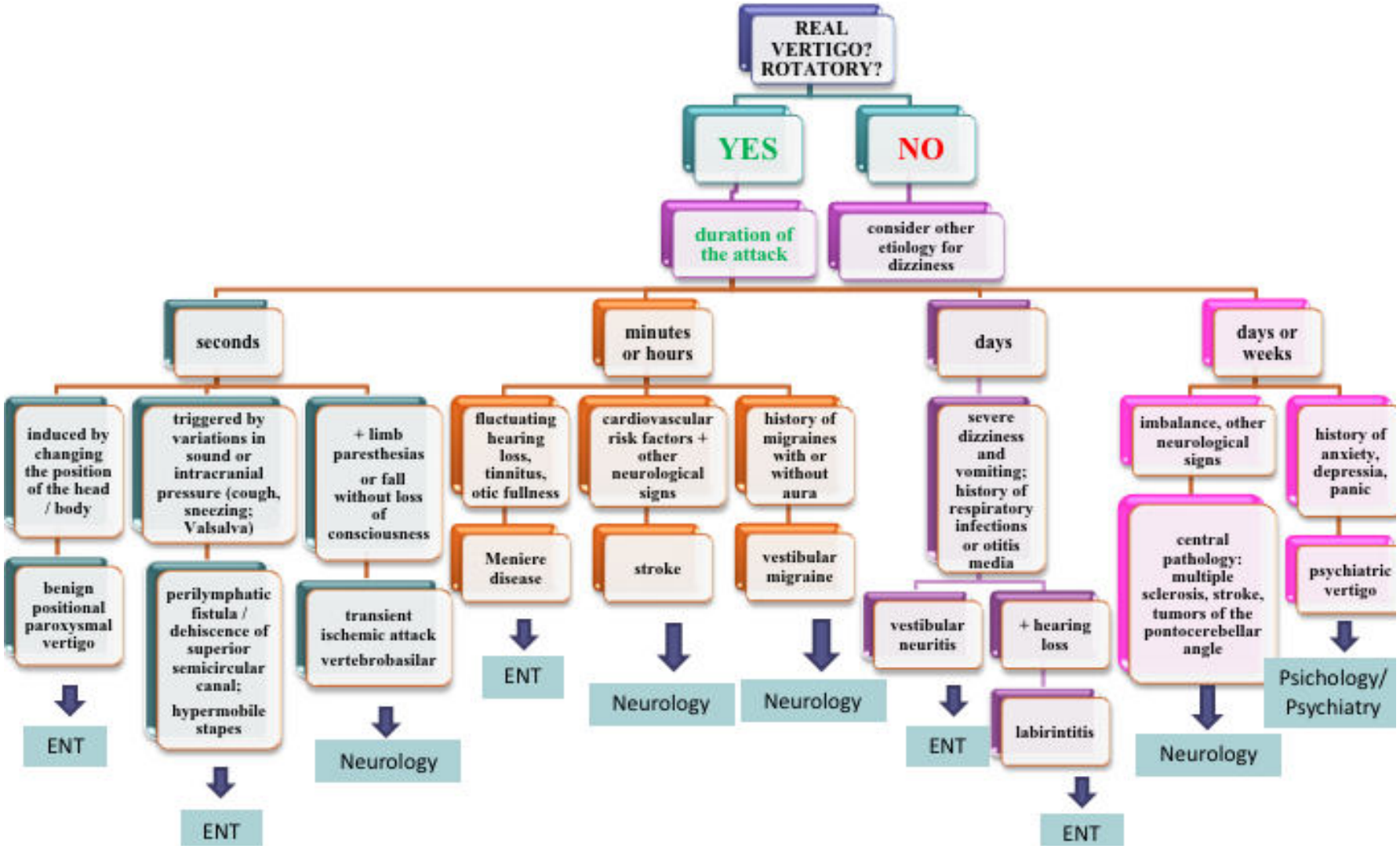


Fig.I.3-1.2.Anamnestic guidelines for clinical diagnosis (interdisciplinar consensus - Romanian Society of Neuro-Otology, 2013)

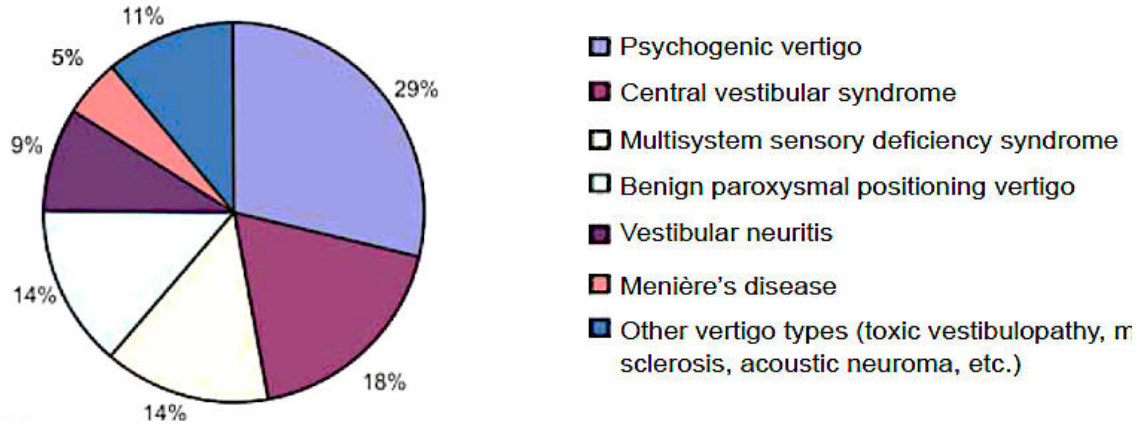


Fig. I.3-1.1. Relative frequency of different vertigo syndromes in neurological practice

Several clinical pictures of different aetiologies include vertigo and dizziness as underlying complaint. Diagnosis should be based on clinical history and neurotological evaluation. A patient can experience more than one type of vertigo and dizziness. There are no defined rules in clinical practice concerning vertigo and dizziness, medical reasoning should be dynamic and flexible, adequate of each individual case (Ganança et al., 2006).

The present study allowed us to develop an algorithm for diagnosing dizzying syndromes and orienting the patient to the most appropriate specialty depending on symptoms, history and evolution (Fig. I.3-1.2).

I.3.1.2. The contribution of vestibular evoked myogenic potentials to the diagnostic of the otolitic pathology

Vestibular Evoked Myogenic Potentials (VEMP) are recorded in the sternocleidomastoid muscles for saccular function (cervical VEMP - cVEMP) and in the periocular muscles for utricular function (ocular VEMP - oVEMP). They are obtained by vibratory vestibular stimulation (high intensity sounds) and are represented graphically by complexes of positive and negative waves (P1 and N1) with latencies between 13-30 ms (Colebatch, Halmagyi, 1992, Colebatch et al., 1994a, 1994b). These tests allow the unilateral exploration of each of the linear acceleration sensors. One of the first fields of application was that of the Superior Canal Dehiscence Syndrome where the evocation threshold of these potentials is considerably low (Hunter et al., 2016). Selective evaluation of vestibular nerve branches is an advantage in studying the evolution of acoustic neurinoma (Matsuzaki et al., 1999, Murofushi, 1998). Selective utricular deficiency may be a risk factor for recurrence of BPPV (benign paroxysmal positional vertigo). In the case of Meniere's disease about 50% of patients have saccular hyporeflexia/ areflexia, even in cases of normoreflexia at the caloric test (Berardino et al., 2014, Maxwell et al., 2016). The absence of VEMP potentials can be a sign of neurological pathologies such as multiple sclerosis, neuropathies, neuromuscular diseases, etc.

Purpose of the study

The aim of the study is to evaluate the utility of VEMPs in establishing the location of the lesion in vestibular syndromes. In these pathologies, the persistence of long-term imbalance is a real cause of decreased quality of life of the patient.

Materials and methods

The retrospective study was performed on a group of 82 patients with peripheral vestibulopathies, selected from the 127 patients diagnosed with vestibular syndrome, who

addressed us in a period of 3 months. They benefited from a complex audio-vestibular evaluation that included testing of otolith function by cVEMP and oVEMP. The standard recording conditions were respected: acoustic attenuated medium, patient lying on the examination bed, preparation of the skin surface and application of contact electrodes in the median frontal area, bilateral retroauricular and in the middle third of the sternocleidomastoid muscle (SCM) for cVEMP and periocular area (infraorbital) for oVEMP. Sound stimulation was achieved through insert headphones.

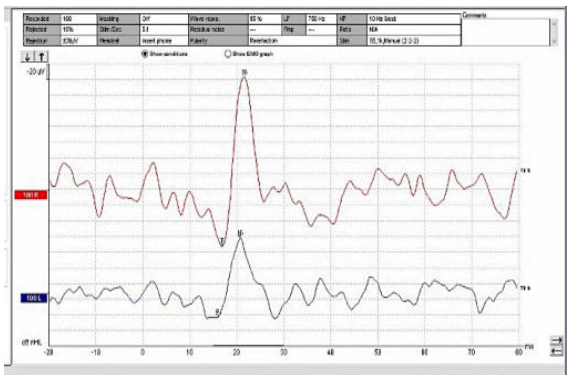


Fig. I.3-1.3. cVEMP wave (red - right saccular response, blue - left saccular response - left saccural hyporeflexia)

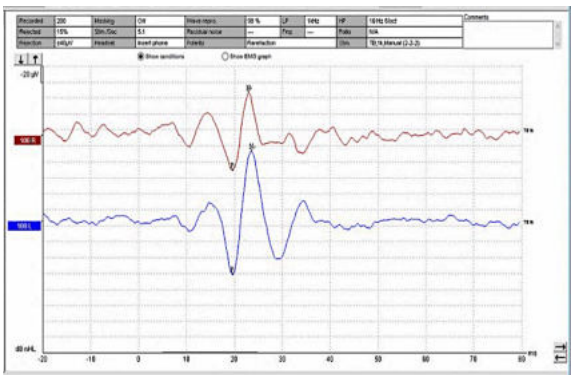


Fig. I.3-1.4. oVEMP example (red - the right utricle response, blue - the left utricle response - right utricular hyporeflexia)

The follow-up response was the biphasic P1-N1 complex recorded after sound stimulation at 100 dB with 1000 Hz burst tons, which is a vibrational stimulus for the utricle and saccula. The analysis of VEMP waves was followed by the presence of characteristic P1N1 complexes, evaluating their latencies and amplitudes. (fig. I.3-1.3 și fig. I.3-1.4).

Results

The analysis of the 127 patients with vestibular syndrome showed that peripheral vestibulopathy is the predominant pathology (82/127 - fig. I.3-1.5. The group of patients with peripheral vestibular deficiency included the following types of conditions: BPPV (37/82), classical vestibular neuronitis (20/82), isolated saccular (7/82) and utricular sensory deficits (5/82), Meniere's disease (5/82), acoustic neurinoma (2/82), neuro-vascular conflict (NVC) (3/82), bilateral vestibulopathy (3/82) (fig. I.3-1.5 și fig. I.3-1.6). VEMP contributed to the confirmation of the diagnosis in the case of 5 compensated vestibular neuronitis without obvious canal deficit in the *head impulse test.*

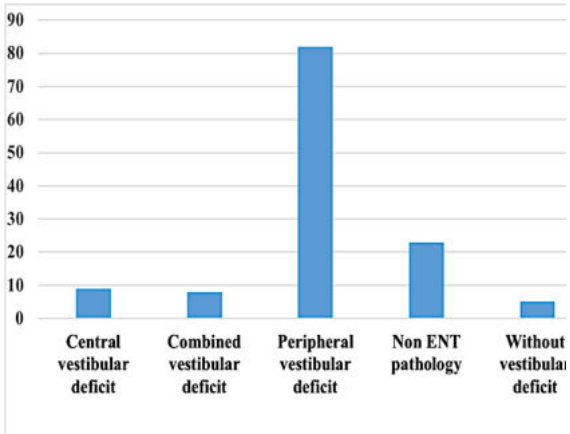


Fig. I.3-1.5. Analysis of the determining lesion of the vestibular syndrome

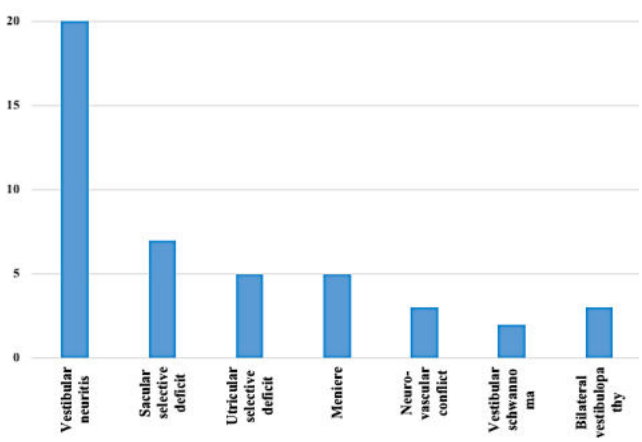


Fig. I.3-1.6. Analysis of the etiology of vestibular syndrome

Also in 12 cases whose vestibular clinical investigation was negative, but which showed persistence of symptoms attributable to a change in linear sensors, cVEMP revealed a saccular hyporeflexia in 7 cases and oVEMP a utricular hyporeflexia in 5 cases.

Changes in cVEMP and oVEMP were noted in some cases where the history suggested a hemodynamic disorder and was indicated for complete cardiological investigation. Of the 5 cases of Meniere's disease, one case showed saccular hyporeflexia at cVEMP and in another case a utricular hyporeflexia was revealed. In 5 cases of recurrent BPPV, it was considered necessary to perform VEMP and thus a saccular deficit was highlighted. The 2 cases of observation of acoustic neurinoma presented, in addition to latency changes of the acoustic evoked potentials, also saccular/ utricular hypo/ areflexia. Of the three cases of neurovascular conflict, only one showed utricular hyporeflexia.

Discutions

The literature discusses the usefulness of VEMP in various vestibular pathologies. In Meniere's disease it is proposed in recent studies to perform cVEMP and multifrequency oVEMP (500Hz and 1000Hz) and to analyze the amplitude and asymmetry with respect to the contralateral ear (Maxwell et al., 2016). VEMP recording in the most common vestibular pathology, BPPV, is normal in most of the cases, except for some cases of recurrent BPPV due to a sacCular deficit (Berardino et al., 2014). Regarding the study of acoustic neurinoma, VEMP is part of the investigation protocol because it indicates the possible origin of tumor formation in the superior or inferior vestibular nerve and is a predictive factor for the evolution of hearing (Chun-Jiang et al., 2016). Our data are consistent with literature data. In the case of Meniere's disease, only 2 of the 5 patients showed vestibular hyporeflexia at VEMP, this fact can be explained by the different stages of Meniere's disease evolution. In patients with BPPV, VEMP was performed only in complex multicanal cases or with multiple recurrences, thus indicating a saccular deficit as a predisposing factor for BPPV. In the case of neuronitis, the diagnosis was made in the acute phase with a suggestive clinical evaluation, subsequently with a caloric test with hot air to highlight the canal deficit. In cases with persistence of non-specific symptoms (5/20) (swaying, swinging sensation) cVEMP and oVEMP were performed. Thus, saccular / utricular hyporeflexias were registered that justify the clinical manifestations. We can say that VEMP is essential in partial saccular and utricular sensory deficits that manifest clinically as atypical neuronitis (sensation of sinking, earthquake), but in which the clinical evaluation and caloric test are negative. VEMP also contributed to the diagnosis of vestibular deficits in neurovascular conflicts (then radiologically confirmed). In central vestibular syndromes, changes in auditory and vestibular potentials may be useful information in the neurological diagnosis for multiple sclerosis, tumors and neuropathies.

Conclusions

VEMP proved indispensable in identifying partial otolithic sensory lesions, as no other available vestibular testing could have indicated these deficiencies. VEMP is a test that has a very good cost-benefit ratio, non-invasive, reproducible and fast that must be part of the balance of any patient with balance disorders of obvious cause.

I.3.1.3. The contribution of computerized dynamic posturography in diagnostic and treatment of vestibular disorders

Introduction

The patient with bilateral vestibulopathy is a complex patient, and posturography has a role both in making a correct diagnosis and in rehabilitation of the bilateral vestibular deficit (Furman, 1994, Furman, 1995). In about 1-4% of cases of vertigo there is a bilateral vestibular deficit (Zingler et al., 2009).The deficit can be total (areflexia) or partial (hyporeflexia). Its most common causes are: administration of ototoxic drugs, post-meningitis lesions, bilateral

Menière's syndrome, bilateral vestibular neuronitis, autoimmune diseases, familiar forms associated with migraine, association with forms of auditory neuropathy (Zingler et al., 2008, 2009, Rinne et al., 1998). The clinic manifestations of this pathology is mainly represented by chronic imbalance, oscillation, difficulty in maintaining postural control or walking with closed eyes (Gillespie, Minor, 1999).

Computerized Dynamic Posturography (CDP) is a tool for assessing the function of balance whose principle is based on the successive exclusion of the inputs of the balance system (vestibular, visual, proprioceptive) by exposing the patient to different test conditions. The analysis of the oscillations of the patient in a vertical position is performed by detecting the forces exercised by the body on platforms equipped with pressure sensors, on the antero-posterior (AP) and medial-lateral (ML) axes. The results obtained represent a quantification of the vestibular deficit isolated or associated with other deficits of the systems involved in postural control. The posturography platform is also used in the treatment protocol of these patients, as its software has exercises with progressive difficulty. This speeds up the deficit compensation process and activates new new strategies for postural control (Hain et al., 2013, Miffon, Guyot, 2015, Tighilet et al., 2009, 2014).

Aim

The purpose of the study is to evaluate the contribution of the computerized dynamic posturography to the diagnosis and compensation in patients with peripheral bilateral vestibular deficiency.

Material and methods

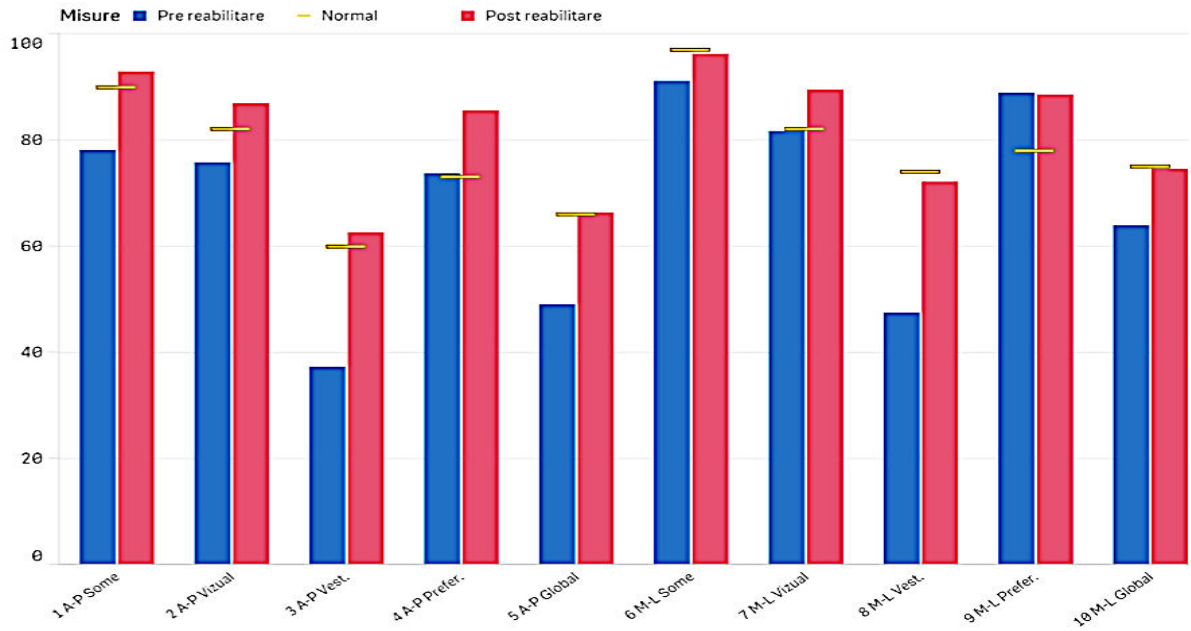
The study is retrospective, including 9 patients, aged between 23 and 74 years, who were initially tested and then followed the vestibular rehabilitation program between 2014 and 2016. The inclusion criteria were: the presence of a symptomatic bilateral deficit, persistent after drug treatment, measurable. The audiovestibular test battery for diagnostic purposes included: static and dynamic tests, CDP, registration of myogenic potentials with vestibular origin (cervical - cVEMP and ocular - oVEMP) and in selected cases the air stimulation caloric test. Within this evaluation, the posturographic recording for diagnostic purposes was the initial and final quantification tool of the isolated or mixed vestibular deficit. Patients followed a therapeutic protocol that included combining drug treatment with betahistine, 48 mg daily, one month, with specific exercises at home, supplemented by vestibular rehabilitation sessions (one session at about 3 days, 10 sessions) using strategies available in within the posturography system. The postural rehabilitation sessions lasted between 20-30 minutes, depending on the complexity of the exercises and the patient's skills. A Synapsis® posturography system was used, which analyzes the three inputs of the vestibular system (vestibular, visual and proprioceptive) through SOT (Sensory Organization Test). Different parameters are analyzed, and by comparing with the values of normality a score is obtained. Thus, a sensory analysis is performed on the two axes: antero-posterior and medial-lateral, which guides the diagnosis to the vestibular impairment model, isolated or associated. The database included the scores obtained by the 9 patients on all types of input, evaluated on the antero-posterior and medial-lateral axes, both in the initial phase and after the posturographic rehabilitation.

Results and discussion

In only one case was there an isolated vestibular deficit, the rest showing a pattern of multisensory impairment. Following the treatment protocol, this patient with isolated vestibular deficit showed a complete recovery of the deficit.

For the group with multisensory impairment, we chose as reference testing for following the evolution of the vestibular compensation the SOT score regarding the vestibular input. At

the end of the rehabilitation period, 4 patients reached the normal range of parameters on both test axes (AP and ML). In the case of 4 other patients, there was a substantial increase in the followed values. These 4 patients in the diagnostic phase presented an average of vestibular scores of 23.5 on the AP axis and 31.25 on the ML axis. At the successive rehabilitation controls, the average vestibular scores were 57.25 (normal score 60) on the AP axis and 61.5 (normal score 74) on the ML axis. Therefore, 5 of the patients obtained a normalization of the score regarding the vestibular input. In the other 4 patients, a substantial improvement of the vestibular parameters was found, associated with the significant improvement of the symptoms, without normalizing. Comparing the average scores of the 9 patients on all types of input and on the two axes AP and ML (Fig. I.3-1.7.) an improvement is observed in the post-rehabilitation phase compared to the evaluation in the pre-rehabilitation phase.



* from left to right:
A-P Some - proprioceptive input A-P axis/A-P Visual – visual input A-P axis/A-P Vest. - Vestibular Input A-P axis /A-P Prefer. - preferentiall input A-P axis /A-P Global - global input A-P axis
M-L Some - proprioceptive input M-L axis/ M-L Visual – visual input M-L axis/ M-L Vest. - Vestibular Input M-L axis / M-L Prefer. - preferentiall input M-L axis / M-L Global - global input M-L axis

Fig. I.3-1.7. Evaluation of posturographic results after rehabilitation on the PDC platform (blue: before, red: post-rehabilitation; n = 10)

Conclusions

The detailed evaluation of the patient before the rehabilitation / reeducation cycle is extremely important for establishing a correct protocol, with a real prognosis. In the case of patients with vestibular hyporeflexia, a reeducation is proposed, taking into account the diagnosis made and the still functional vestibular structures. In patients with vestibular areflexia, the compensation may be much slower (Black et al., 2000), requiring extended periods with postural rehabilitation sessions.

Computerized dynamic posturography is a simple and rapid method that can give mesurable information by analyzing the sensory model developed in the evaluation of the patient with vestibulopathy. Also, its use in the rehabilitation of the patient with vestibular deficit leads to the acceleration of better postural control regaining, to reduce the falling risk and to improve the patient's quality of life (Badke et al., 2005).

I.3.2. Research of the vestibular stress effects on the cardiovascular reactivity

Introduction

The vestibular acute stress induces reversible alert-like reactions that involve the sympathetic adrenal-medullar system and hypothalamic-pituitary-adrenal axis responses.

Several studies have examined the autonomic effects of vestibular stimulation, suggesting that vestibular imbalance is a stressful condition in itself (Saman et al., 2012) and caloric vestibular test (CVT)-evoked vertigo may generate some uneasiness in patients, eliciting an acute and reversible alert-like reaction that involves the sympathetic adrenal-medullar (SAM) system and hypothalamic-pituitary-adrenal (HPA) axis responses. Measurements of salivary α-Amylase (α-Amy) and cortisol as neuroendocrine subclinical indicators of the SAM system and HPA axis activities are increasingly used for not invasive monitoring of the response of the human body to stressful challenges under different physio-pathological conditions (Bosch et al., 2011, Cozma et al., 2017, Delle Chiaie et al., 2013, Ghiciuc et al., 2011, 2013, 2016, Nater et al., 2013, Patacchioli et al., 2015, Schumacher et al., 2013, Simeoni et al., 2011).

Main articles published in this field:

- **Cozma S**, Ghiciuc CM, Damian L, Pasquali V, Saponaro A, Lupusoru EC, Patacchioli FR, Dima-Cozma LC. Distinct activation of the sympathetic adreno-medullar system and hypothalamus pituitary adrenal axis following the caloric vestibular test in healthy subjects**.** *PLoS One.* 2018; 13(3): e0193963. doi: 10.1371/journal.pone.0193963. eCollection 2018. (IF=2,776)

Scientific contributions /Clinical implications:

- This study shows a correspondence of variations in cortisol and alphaamylase associated with the effects induced in the cardiovascular system by vestibular stimulation, which is a stress factor. It is one of the few studies of this kind and the first to establish a significant inverse relationship between the production of alpha-Amy and cortisol elicited through the air-CVT task.

Aim of research

We hypothesized that the air CVT-evoked vertigo challenge alters salivary α-Amylase and cortisol production. The study subjects were investigated under the basal condition and at various times for 60 minutes after reaching the time of maximal nystagmic reaction following caloric irrigation. The present study was conducted with a twofold purpose: to simultaneously evaluate cardiovascular activity during the aversive acute task of the air CVT stimulation by measuring several cardiovascular parameters in the study population, including heart rate (HR), R to R wave interval (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), which were recorded while measuring the salivary biomarkers.

Materials and methods

Study population. A total of 62 moderately active (moderate physical activity not exceeding > 2 hours and 30 minutes spread throughout the week), healthy Caucasian males were recruited among students attending the Iași Universities. For all subjects, the medical examinations, main hematological and blood chemistry parameters, and electrocardiograms were within normal ranges; metabolic, cardiovascular, endocrine and other chronic diseases were considered as the exclusion criteria. Later, 12 subjects were excluded because they incorrectly collected the salivary samples, and 2 because they occasionally took drugs that were not allowed in the three days preceding the experimental procedure.

Experimental protocol

We organized 3 subsequent experimental sessions. In the first session, they underwent baseline cardiac evaluations (with electrocardiogram) and an ENT physical examination to check the anatomical integrity and functionality of the audio-vestibular system.

In the second session, we performed a psychometric screening of the study population to exclude any psychopathologies and to measure individual subjective stress perception scores in the study population (Hamilton Rating Scale for Depression (HDS) (Hamilton, 1960), the Hamilton Anxiety Rating Scale (HAS) (Maier et al., 1988), the Perceived Stress Scale (PSS) (Cohen, Williamson, 2008). Stress level perceptions were also indicated by the Hassles questionnaire scores, which were recorded after the air CVT challenge and compared with those reported during the enrollment session (Kohn, Macdonald, 1992).

At the end of the second session, all subjects were taught how to collect their saliva at home using the Salivette sampling device (Sarstedt, Germany) (Simeoni et al., 2011). The day after the home saliva collection, the subjects attended the third experimental session (always in the morning between 9:00 and 12:00), when the air CVT was performed, according to the British Society of Audiology guidelines 2010 (British Society of Audiology) and Gananc and coworkers (Ganança et al., 2009). The air CVT stimulation was performed by irrigating the external auditory canal of the right ear with a flow of 50˚C warm air (Air Fx Caloric stimulator, Interacoustics, Denmark) for 60 seconds (Kasbekar et al., 2010). After air irrigation and observation of the nystagmus, the patients were asked to rate the level of their symptoms of dizziness on a Likert scale (Duracinsky et al., 2007).

Ten minutes before the air CVT task, the subjects were attached to a 12 channel Holter (BTL-08 CardioPoint-Holter, USA) for continuous monitoring of the electrocardiogram. The SBP and DBP were measured using a semi-automatic sphygmomanometer (M3; Omron, Matsusaka Co. LTD, Japan). MAP was calculated as (2DBP + SBP)/3 (Katz, Ruoff, 2014). Salivary samples were collected 5 minutes before the CVT task (under the basal experimental condition) and 1, 4, 7, 10, 15, 30, 45 and 60 min thereafter, at the same time as the cardiovascular measurements. At all these experimental session time points, the SBP and DBP were sequentially determined, while the corresponding HR and R to R wave interval were selected from the Holter recording. At the end of the CVT task session, PSS questionnaires were administered to measure the self-perceived stress impact induced by the task, and individual scores were compared with those measured on the enrollment day.

Saliva collection. and salivary biomarker assay

Saliva was collected using the Salivette sampling device (Sarstedt, Germany), which allows for quick and hygienic saliva recovery from a polyester swab through centrifugation at 3,000 rpm for 15 min (Ghiciuc et al., 2011). Salivary samples were immediately frozen at –20˚C until the analysis. α-Amy and cortisol assays were performed, as previously described (Ghiciuc et al., 2011), using commercially available assay kits (Diametra, Italy).

Data analysis and statistic

Unless otherwise specified, the data are reported as the mean ± SD. Statistical analyses and graphics were performed using the Sigma Plot 11 (SxST.it, Italy) and Statistica 6.0 (Statsoft Inc, USA) software programs. A repeated measures ANOVA test was performed to reveal the diurnal variation of the α- Amy and cortisol secretions and the effect of air CVT on the salivary cortisol and α-Amy concentrations, as well as on SBP, DBP, HR and RR, which were simultaneously recorded with the salivary collections during the air CVT task. To evaluate the trend of each salivary biomarker production in the 15 min following the air CVT stress-induced response, Pearson's coefficient for salivary biomarker concentration against time was determined; when the resulting r value was significant, an equation that described the interpolated regression line was derived, and Student "t" test for slope comparisons was applied (Aiken, West, 1991, Cohen et al., 2003). The statistical significance was set at $p<0.05$.

Results

Characteristics of the study population. At the time of enrollment, somatic and psychometric characteristics of the study population were: the body mass index (BMI), which compares height to weight was within the normal range and waist circumference, an indicator of cardiometabolic risk, showed that the study population was below 94 cm, the lower risk level for men (Yumuk et al., 2015); the basal cardiovascular parameters (SBP, DBP and HR) were within the normal range; HDS (<7) and HAS (<20) scores indicated no signs of depression or anxiety.

Fig I.3-2.1 (upper part) shows the mean levels (±SE) of α-Amy measured in the study population at 08:00 h, 12:00 h and 20:00 h during a resting day. The one-way repeated measures ANOVA revealed significant effects for the factor time $F(2,143) = 19.809$, $p<0.001$. The post hoc Fisher LSD method for multiple comparisons showed that the α-Amy diurnal pattern, with levels measured at 08:00 h, was significantly lower than those measured at 12:00 h and at 20:00 h. Fig I.3-2.1 (lower part) shows the mean levels (±SE) of salivary cortisol measured in the study population during a resting day. The one-way repeated measures ANOVA revealed significant effects for the factor time $F(2,143) = 135.843$, $p<0.001$. The post hoc Fisher LSD method for multiple comparisons showed that the salivary cortisol concentrations measured at 12:00 h and 20:00 h were significantly lower than those measured at 08:00 h.

Air CVT-evoked nystagmus, dizziness and stress perception in the study population. The latency (41±2 seconds) and the duration of the nystagmus (127±28 seconds) were measured in the participants as an objective sign of the induced vertigo. As a subjective uneasiness symptomatology induced by the air CVT challenge, a quite intense sensation of dizziness (7.5± 2, on a 10-point Likert scale) was reported by the study participants.For the PSS questionnaire, the participants demonstrated a score (29±3) indicated that they perceived a low level of stress during the enrollment session at the end of the air CVT task, they showed signs of a medium level of stress perception, with individual scores significantly higher (Wilcoxon signed-rank test, $z = 6.043$, $p<0.001$). A medium stress level perception was also indicated by the Hassles questionnaire scores after the air CVT challenge, compared to the low stress level perceived during the enrollment session (Wilcoxon signed-rank test, $z = 6.046$, $p<0.001$).

Air CVT-evoked change in α-Amy and cortisol production in the study population. Fig I.3-2.2 (upper part) shows the mean (±SE) α-Amy levels measured in the study population before the air CVT challenge and at various times thereafter (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects at various times after the air CVT challenge $F(8,431) = 13.584$, $p<0.001$. The Tukey test showed that the α-Amy concentrations measured after the end of the air CVT task were significantly lower than those measured before the task. Fig I.3-2.2 (lower part) shows the mean (±SE) salivary cortisol measured in the study population before the air CVT challenge and at various times thereafter (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects at different times after the air CVT challenge $F(8,431) = 4.432$, $p<0.001$. The post hoc Tukey test showed that the salivary cortisol concentration measured after the end of the air CVT task were significantly higher than the levels measured before the task.

Correlation between air CVT–evoked α-Amy and cortisol production in the study population. The effect of the stressor was significant during the first 15 min following the air CVT stimulation. Therefore, to evaluate the trend of each salivary biomarker production during this period, Pearson's coefficient for salivary biomarker concentration against time was determined. Because the resulting r values were significant, an equation describing the interpolated regression line was derived. The results (scatterplots are not shown) showed the following regression lines for α-Amy ($N = 288$): $y_{\alpha\text{-Amy}} = 27.6618 – 0.4195x$ ($r = -0.2023$, $p = 0.00055$). The following regression lines were demonstrated for salivary cortisol ($N = 288$): $y_{Cortisol} = 3.7387 + 0.0774x$ ($r = 0.198$, $p = 0.000715$). The t-tests for the slope of the α-Amy

line vs the cortisol line (slope α-Amy = -0.4195; slope Cortisol = 0.0774) yielded a $p<0.001$ statistically significant difference, with $t = -3.283$ (DF = 575), indicating that parallelism was not present among the lines. Thus, the results showed that while α-Amy production decreased after stress, salivary cortisol production increased.

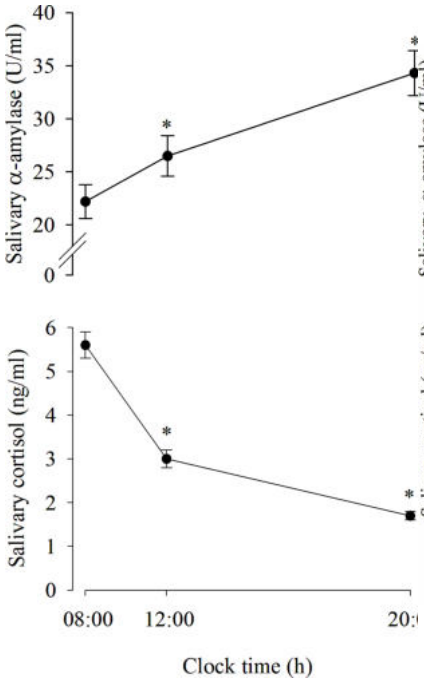


Fig. I.3-2.1. Diurnal trajectories of salivary α-amylase and salivary cortisol during a rest day. Data are expressed as the mean±SE. m: $p<0.001$ vs 08:00.

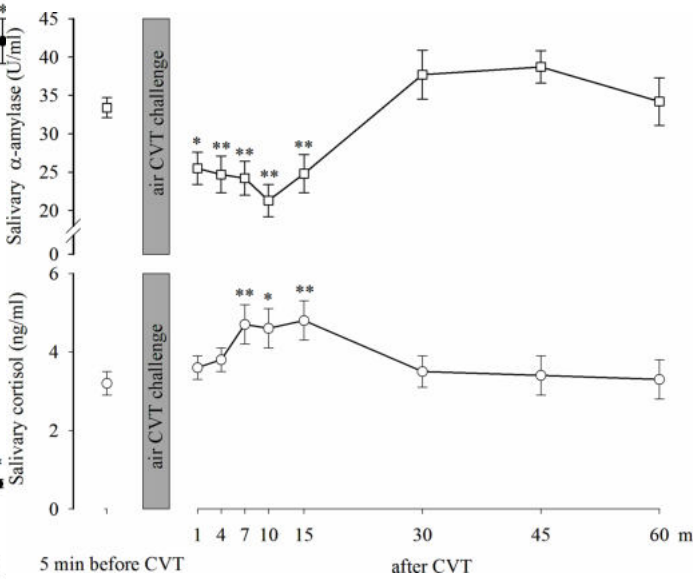


Fig. I.3-2.2. Diurnal trajectories of salivary α-amylase and cortisol before and after CVT stimulation. Data are expressed as the mean±SE.
*,**: $p<0.01$ and $p<0.001$, respectively, vs before the CVT.

Air CVT-evoked cardiovascular activity changes in the study population. Fig. I.3-2.3. (upper part) shows the HR in the study population before and at various times after the air CVT task (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed that significant effects were induced by the air CVT challenge during the time thereafter $F(8,431) = 27.027$, $p<0.001$. The post hoc Tukey Test showed that the HR measured 1 min after the end of the air CVT challenge was significantly higher than that measured before the task. In contrast, the HRs measured (7 min, 10 min and 15 min) after the end of the air CVT task were significantly lower than those before the test. Fig. I.3-2.3. (lower part) shows the RR interval in the study population before and at various times after the air CVT task (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects induced by the air CVT challenge during the time thereafter $F(8,431) = 26.262$, $p<0.001$. The post hoc Tukey test for multiple comparisons showed that the RR interval measured 1 min after the air CVT challenge was significantly lower than that measured before the task. In contrast, the RR intervals measured 7 min, 10 min and 15 min after the end of the air CVT task were significantly higher than those measured before the test.

Fig. I.3-2.4. (upper part) shows the SBP in the study population before the air CVT challenge and at various times thereafter (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects induced by the air CVT challenge during the time thereafter $F(8,431) = 11.179$, $p<0.001$. The post hoc Tukey test showed that the SBPs measured 10 min and 15 min after the end of the air CVT task were significantly lower

than those measured before the task. Fig. I.3-2.4. (middle part) shows the DBP levels in the enrolled subjects before the air CVT challenge and at various times thereafter (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects induced by the air CVT challenge during the time thereafter $F(8,431) = 5.370$, $p<0.001$. The post hoc Tukey test showed no significant effects on DBP compared with those measured before the task in the study population. Fig. I.3-2.4. (lower part) shows the MAP calculated in the enrolled subjects before the air CVT challenge and at various times thereafter (1, 4, 7, 10, 15, 30, 45 and 60 min.). The one-way repeated measures ANOVA revealed significant effects induced by the air CVT challenge during the time thereafter $F(8,431) = 8.069$, with $p<0.001$. The post hoc Tukey test showed that the MAPs measured 7 min, 10 min and 15 min after the end of the air CVT task were significantly lower than those measured before the task.

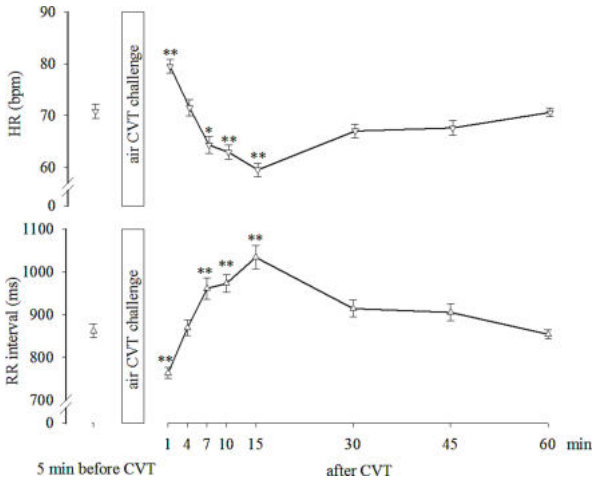


Fig. I.3-2.3. HR and RR intervals before and after the CVT stimulation. Data are expressed as the mean±SE. m, mm: $p<0.01$ and $p<0.001$, respectively, vs before the CVT.

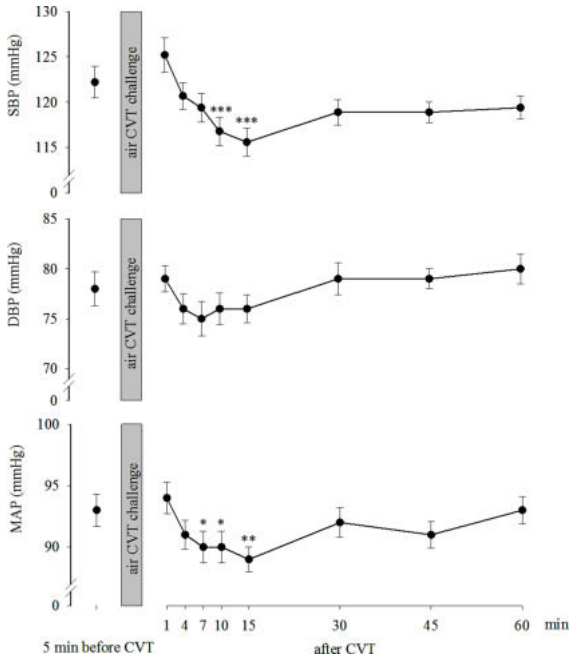


Fig. I.3-2.4. SBP, DBP and MAP before and after the CVT stimulation. Data are expressed as the mean±SE. m,mm,mmm: $p<0.05$, $p<0.01$ and $p<0.001$, respectively, vs before the CVT.

Discussion

We hypothesized that the air CVT-evoked vertigo challenge provokes alterations in α-Amy and cortisol production. Here, we report that the cortisol variation generated by the exposure to the air CVT-evoked vertigo in healthy young subjects was consistently associated with an alarm reaction in the HPA axis and a reduction in sympathetic activity, as shown by the reduced α- Amy secretion. Thus, the two systems act distinctly in response to stress, which has been previously shown in asthmatic children (Wolf et al., 2008) and in maltreated youth (Gordis et al., 2008). Furthermore, the transitory stress-induced modifications of the salivary biomarkers were associated with consistent transient changes in HR, SBP and MAP during the time following the vestibular stimulation.

In the present study, we demonstrated that the air CVT, a useful medical examination procedure that assesses the horizontal semicircular canal function of each labyrinth and is severe enough to provoke nystagmus and dizziness, is a powerful activator of the HPA axis, a finding that aligns with previous observations made by Dagilas and coworkers (Dagilas et al., 2005).

Under basal non-challenging conditions, the study population showed the expected significant diurnal fluctuation of salivary cortisol levels and α-Amy, having opposite patterns: as evening approaches, cortisol concentrations decrease, and α-Amy activity increases (Ghiciuc et al., 2011, Nater et al., 2013). Overall, salivary cortisol levels reflect the activity of the HPA axis, whereas α-Amy is a marker of the sympathetic activity. Using air CVT task as a stressor, the present study indicates a connection between the acute hormonal stress response to vestibular stimulation and cardiovascular output. Several clinical observations and animal studies have suggested a link between vestibular and autonomic systems (Yates, Miller, 1994, Dagilas et al., 2005, Biaggioni et al., 1998, Costa et al., 1995). Rather than a sympathetic inhibition, vestibular stimulation has consistently been shown to increase the sympathetic outflow in cardiac and splanchnic vascular beds in most experimental models (Saman et al., 2012, Yates, Miller, 1994) or even to induce inconsistent changes in HR and BP, despite substantial symptoms of motion sickness in humans (Biaggioni et al., 1998).

Our study aligns with other previously published papers that have reported that stress-dependent variations in α-Amy occurred in conjunction with cardiovascular parameter responses, reflecting autonomic function (Patacchioli et al., 2015, Chatterton et al., 1996, Nater et al., 2006, Kang, 2010, Akizuki et al., 2014). We reported a significant decrease in HR, SBP and MAP during the first 15 minutes of observation following the air-CVT challenge, as well as an increase in the pretest values thereafter, which aligned with the α-Amy response.

The protocol of the present study provided a multiple time point assessment of the salivary biomarkers of SAM system and HPA axis and different parameters of cardiovascular activity after CVT challenge, which is consistent with a distinct activation of the two systems and the HR, SBP, DBP and MAP, showing the same trend changes with α-Amy. Salivary cortisol levels increased during the first 15 minutes following the CVT, likely secondary to the stressful state induced in the study population by the vestibular stimulation.

Although many previous studies have investigated the link between the HPA axis and sympathetic activities in response to different stressful tasks, the complex reciprocal counterbalances have not been entirely defined in terms of the timing and modalities of their activation and interactions (Cozma et al., 2017, Ali, Pruessner, 2012, Cortelli et al., 2012). No correlation between α-Amy and cortisol responses and various stress paradigms have been reported (Ali, Pruessner, 2012, Takai et al., 2004). In contrast, we found a significant inverse relationship between the production of α-Amy and cortisol elicited through the air-CVT task.These discordant outcomes may be related to different stress paradigms or to differences in some characteristic of the population sampled: here we enrolled young healthy male subjects with no signs of depression and anxiety (Hackney, Viru, 2008). Furthermore, the discrepancy may be related to the different statistical analyses used.

However, though future studies will be conclusive, the data presented by us could further support these hypotheses because of the peculiar α-Amy response to the vestibular stimulation, which is aligned with the reduced cardiovascular output.

Conclusions

Previous studies from our group and others have shown that the measurement of salivary cortisol and α-Amy is becoming more widely accepted for monitoring changes in HPA and SAM activity under stress-related conditions (Cozma et al., 2017, Simeoni et al., 2011, Damian et al., 2016, Kirschbaum, Hellhammer, 1994, Patacchioli et al., 2003, 2006, Pippi et al., 2014). Changes in salivary cortisol and α-Amy, as well as their diurnal fluctuations, are thought to have health implications (Wolf et al., 2008, Ahn et al., 2007, Chida, Steptoe , 2009, Patacchioli et al., 2014).

The interactions between stress and vestibular functions have been investigated in animal models and in clinical studies (Saman et al., 2012, Archana et al., 2016) and the possible functional consequences of the consistent SBP, MAP and HR changes evoked by vestibular

stimulation have been reported in a healthy population (Hallgren et al., 2015). We cannot exclude that activating component of vestibular apparatus different from those activated in the present study by CVT might elicit different somatic (muscle, skin, cardiovascular output, etc) and neuro-endocrine responses (Hammam, Macefield, 2014). Further research is needed before we can establish the potential importance of vestibular input to cardiovascular regulation and orthostatic tolerance in humans.

I.3.3. Research on Meniere's disease terapeutic strategies : intratympanic dexamethazone plus high dosage of betahistine

Introduction

Meniere's disease (MD) is pathophysiologically regarded as an endolymphatic hydrops of unknown etiology (Sajjadi, Paparella, 2008). Clinical diagnosis is established on a history of spontaneous vertigo spells, fluctuating sensorineural hearing loss, tinnitus, and aural fullness (Minor et al., 2004, Merchant et al., 2005). Most often, vertigo is incapacitating, and thus, management is primarily intended to decrease the incidence and severity of vertigo. The management protocol typically comprises dietary recommendations such as a low sodium diet and restriction of caffeine, nicotine, medications and, as a last remedy, surgical approaches (Coelho, Lalwani, 2008). Medical treatment includes diuretics, betahistine, intratympanic (IT) injection of gentamicin or corticosteroids (Sajjadi, Paparella, 2008, Merchant et al., 2005). Quite a lot of papers on betahistine for MD have been issued presenting conflicting results (Jeck-Thole, Wagner, 2006, James, Burton, 2001, Nauta, 2014). However, an open trial proved that higher-dosage of betahistine (144 mg/day) is capable to significantly decrease incapacitating vertigo spells in MD (Strupp et al., 2008) Recently, IT corticoids injections became widespread in clinical practice mainly because minimal side effects were reported in relationship to their use (Itoh, Sakata, 1991, Shea, Ge, 1996, Garduno-Anaya et al., 2005, Silverstein, 1998, Barrs et al., 2001, Barrs, 2004, Boleas-Aguirre et al., 2008). IT corticosteroids achieve greater inner ear concentrations than those acquired through systemic administration (Parnes et al., 1999). Although IT gentamicin affords superior vertigo control compared with IT corticoids, it carries a greater risk of hearing loss and imbalance (Casani et al., 2012). This is why in clinical practice it appears that IT corticoid injections are extensively prescribed (Boleas-Aguirre et al., 2008). Some studies have presented encouraging results, while others reported unsatisfactory outcomes associated with IT corticoids (Itoh, Sakata, 1991, Shea, Ge, 1996, Garduno-Anaya et al., 2005, Silverstein, 1998, Barrs et al., 2001, Barrs, 2004, Boleas-Aguirre et al., 2008, Parnes et al., 1999, Casani et al., 2012).

Main articles published in this field:

- Albu S, Nagy A, Doros C, Marceanu L, **Cozma S**, Musat G, Trabalzini F. Treatment of Meniere's disease with intratympanic dexamethazone plus high dosage of betahistine. *Am J Otolaryngol.* 2016; 37(3): 225-230. (IF=1,033)

Scientific contributions /Clinical implications:

- The research emphasizes the effectiveness of vertigo control using the combined treatment: high doses of betahistine and transtympanic dexamethasone, the effect of ITD being immediate while HDBH needs longer time to achieve decrease in vertigo spells. By contrary, there were no significantly effects on hearing levels and tinnitus scores with this combination.

Purpose of research

The aim of the present study was to assess if the combined therapy of intratympanic dexamethasone (ITD) and high dosage of betahistine (HDBH) is able to provide increased vertigo control compared to ITD alone in patients suffering from definite unilateral Meniere's disease (MD).

Materials and methods

A multicenter, prospective study assessing the effectiveness of the combined HDBH and ITD in decreasing vertigo spells in MD was performed between January 2009 and June 2013. Five departments with extensive experience in vestibular pathology were involved, 4 from Romania and one from Italy (Siena). Inclusion criteria were: adult patients with unilateral definite MD according to the guidelines of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (AAO-HNS, 1995); mean of four or more vertigo spells per month during the 3 months foregoing management (Strupp et al., 2008); failure a trial of 6 months of low-salt diet, dietary restrictions (caffeine and nicotine avoidance). Exclusion criteria were: bilateral MD, other peripheral or central vestibular syndromes, middle ear pathology, noise-induced hearing loss, previous IT gentamicin or corticosteroid or preceding ablative ear surgery and allergy to betahistine. Patients underwent a complete neuro-otologic examination. Auditory testing comprised standard pure tone audiometry (PTA) and speech discrimination score (SDS). The Functional Level Score (FLS), Class and vertigo control (class A–F) were defined according to the AAO- HNS criteria (AAO-HNS, 1995). The Tinnitus Handicap Inventory (THI) was completed in each patient (Newman et al., 1996). All were recorded before the treatment and at the end of the follow-up. Patients with definite MD were offered different therapeutic alternatives: IT injection of corticoid or IT injection of gentamicin and vestibular neurectomy. Patients elected ITD injection with or without HDBH as an opportunity that might provide transitory cessation of vertigo spells without the destruction of vestibular system. If complete or substantial vertigo control was not accomplished, another sequence of ITD was offered. Enrolled patients were divided randomly in two groups (A and B), each comprising 33 patients. Group A received a combination of ITD and identical-appearing placebo pills while Group B received a combination of ITD and HDBH. Dexamethasone was injected under the microscope according to the guidelines (Itoh, Sakata, 1991, Shea, Ge, 1996, Garduno-Anaya et al., 2005, Silverstein, 1998, Barrs et al., 2001, Barrs, 2004, Boleas-Aguirre et al., 2008). Under local anesthesia dexamethasone (4 mg/mL) was injected through a 22-gauge spinal needle and 1-mL syringe to fill the middle ear. The ITD protocol consisted of three consecutive daily injections. HDBH consisted in 144 mg/ day (48 mg tid). All patients kept a diary recording the occurrence of every vertiginous attack. Every patient was monitored for at least 2 years, at 2-month intervals.

Results

Sixty six patients with unilateral definite MD were included in the present investigation. The baseline features of two distinct groups are presented in Table I.3-3.A. The mean number of vertigo attacks per month did not differ between the two groups at baseline: in group A patients suffered a mean of 7.5 vertigo spells per month compared to 6.7 vertigo attacks per month in group B. The difference is not statistically significant. Sixty two patients completed the 24-month follow-up, while 4 patients (1 in Group A and 3 in Group B) were lost to follow-up. In Group A five patients (15%) received 1 ITD reinjection and 6 patients (18%) received 2 re-injections. In Group B four patients (12%) got 1 re-treatment and 3 patients got 2 re-treatments comprising ITD injections. Complete vertigo control was attained in 14 patients (44%) in Group A and in 22 patients (73.3%) in Group B (Table I.3-3.B). The difference is statistically significant, $p = 0.01$ chi square test. The difference between the groups in attaining complete vertigo relief is further demonstrated employing the Kaplan– Meier plot specific to

class A: according to log rank test (p = 0.027) the difference is statistically significant (see Fig. I.3-3.1).

	Group A N = 33			Group B N = 33			p value
Gender							
Males/Females	12/21			15/18			0.46*
Stage	2	3	4	2	3	4	0.83*
Patients (N)	6	18	9	7	19	7	
FLS	3	4	5	3	4	5	0.87*
Patients (N)	4	17	12	5	15	13	
PTA (Mean ± SD)	51.4 ± 13.6			54.6 ± 15.2			0.47**
SDS (Mean ± SD)	65.2 ± 18.6			68.4 ± 17.7			0.73**
THI (Mean ± SD)	27.7 ± 16.7			28.3 ± 14.8			0.81**

Group A: IT dexamethasone.
Group B: IT dexamethasone plus betahistine.
FLS: functional level score.
PTA: pure tone audiometry.
SDS: speech discrimination score.
THI: Tinnitus Handicap Inventory.
* chi square test.
** Student t test.

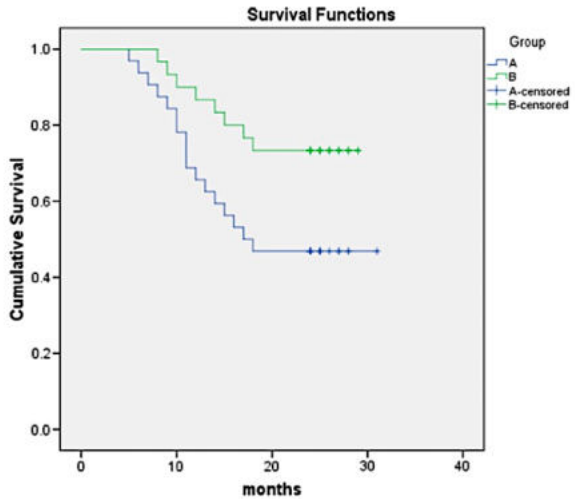
Table I.3-3.A – Distribution of baseline features in the two groups.

	Group A N = 32 (%)	Group B N = 30 (%)	p value chi square test
Class			
A	14 (44%)	22 (73.3%)	0.11
B	7 (22%)	5 (16.6%)	
C	6 (19%)	1 (3.3%)	
D	4 (12%)	1 (3.3%)	
E	1 (3%)	1 (3.3%)	
FLS			
1	15 (47%)	22 (73.3%)	0.04
2	8 (25%)	7 (23.3%)	
3	7 (22%)	1 (3.3%)	
4	2 (6%)	0 (0%)	

Group A: IT dexamethasone.
Group B: IT dexamethasone plus betahistine.

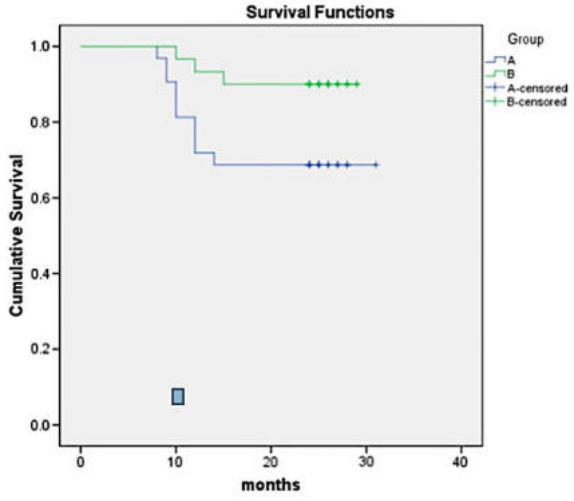
Table I.3-3.B – Vertigo class and functional level in the two groups of patients following treatment.

Substantial vertigo control (class A + B) was obtained in 21 patients (65.6%) in Group A and 27 patients (90%) in Group B. The difference is statistically significant, p = 0.02 chi square test. The Kaplan–Meier plot specific to class A + B validates the significant difference: p = 0.035 log rank test (see Fig. I.3-3.1).



Group A: IT dexamethasone
Group B: IT dexamethasone plus betahistine

Fig. I.3-3.1. – The Kaplan–Meier survival curves for the likelihood of achieving complete (class A) vertigo control in the two groups throughout the study period.



Group A: IT dexamethasone
Group B: IT dexamethasone plus betahistine

Fig. I.3-3.2. The Kaplan–Meier survival curves for the likelihood of achieving substantial (class A + B) vertigo control in the two groups throughout the study period.

In Group A, despite 1 or 2 re-treatments, 10 patients reported limited control (class C and D) and one patient had no control of vertigo (class E). In Group B, 2 patients had limited control (class C and D), while failure was reported in 1 case (class E). Failures in both treatment groups were programmed for IT gentamicin. At 24-month follow-up, level one of FLS was

reached in 15 patients and level 2 in 8 cases in Group A, while in Group B 22 patients achieved level one and 7 patients level 2. The difference is significant, p = 0.04 chi square test.

	Group A N = 32	Group B N = 30	p value student t test
PTA (Mean ± SD)			
Before treatment	51.4 ± 13.6	54.6 ± 15.2	0.47
After treatment	49.8 ± 16.7	51.2 ± 17.4	0.65
p value	0.38	0.73	
SDS (Mean ± SD)			
Before treatment	65.2 ± 18.6	68.4 ± 17.7	0.73
After treatment	63.6 ± 19.8	66.4 ± 20.2	0.68
p value	0.73	0.54	
THI (Mean ± SD)			
Before treatment	27.7 ± 16.7	28.3 ± 14.8	0.81
After treatment	25.4 ± 13.2	26.3 ± 12.7	0.72
p value	0.31	0.46	

Group A: IT dexamethasone
Group B: IT dexamethasone and betahistine
PTA: pure tone audiometry
SDS: speech discrimination score
THI: Tinnitus Handicap Inventory

Table I.3-3.C – PTA, SDS and THI scores before treatment and at the end of the study in the two groups.

Hearing outcomes are listed in Table I.3-3.C. According to our results at the end of the study there were no statistically significant variations within and between the groups. According to the 1995 AAO-HNS guidelines, in Group A hearing was unchanged in 15 patients, improved in 3 patients and worsened in 14 patients. Following the same guidelines, in Group B hearing was unchanged in 16 patients, improved in 2 patients and declined in 12 patients. No difference between the groups in tinnitus awareness was noted. Side-effects associated with HDBH were not significant (nausea in 2 patients, headache in 5 cases, diarrhea in 8 cases). Nevertheless, these adverse effects did not cause disruption of therapy.

Discussion and conclusion

According to animal experiments, betahistine is an H1 receptor agonist and an H3 receptor antagonist and thus modulates synaptic transmission (Lacour et al., 2007). Furthermore, betahistine increases in a concentration-dependent mode the blood flow in the cochlea and in the brain (Laurikainen et al., 1998, Ihler et al., 2012). It additional demonstrated a dose-dependent inhibitory action on spike generation within the neurons located in the medial and lateral vestibular nuclei (Valli, 2000). It is also suggested that betahistine enhances significantly behavioral recovery and vestibular compensation in MD (Nauta, 2014, Strupp et al., 2008, Lacour, 2013). The most recent meta-analysis of 12 randomized, double-blind, placebo-controlled clinical studies, clearly demonstrated a favorable outcome in MD patients treated with betahistine (Nauta, 2014). Additionally, Strupp et al. (Strupp et al., 2008) established that in MD, HDBH is more powerful than low dosage in decreasing the number of vertigo spells. According to previous clinical recommendations (Boleas-Aguirre et al., 2008, Parnes et al., 1999, Casani et al., 2012), we have employed ITD in our trial. Generally speaking, the efficacy of ITD in controlling vertigo in MD patients is disappointingly low (Silverstein et al., 1998, Barrs, 2004, Casani et al., 2012). Better outcomes with ITD might be related to higher dosage (16 mg/mL) than the dosage commonly used (4 mg/mL) or to the use of round window constant delivery systems (Casani et al., 2012). Despite these results, patients chose to continue with repeated IT injections as an alternative to ablative procedures. It was assumed that ITD affords only temporary symptomatic relief and thus needs to be repetitive until the occurrence of spontaneous remission (Boleas-Aguirre et al., 2008, Casani et al., 2012).

In an attempt to improve vertigo control related to ITD, we used HDBH in combination with ITD. Since ITD is a repetitive treatment, it was previously suggested that Kaplan–Meier method provided a perfect exemplification of the clinical course of ITD (Boleas-Aguirre et al., 2008). This is why we reported our results according to both the AAO-HNS criteria (AAO-HNS, 1995) and Kaplan– Meier survival method. We were able to demonstrate that complete vertigo control is significantly higher in patients treated with HDBH and ITD. Additionally, the number of patients attaining substantial vertigo control (class A + B) is statistically higher with the combined treatment. The two medications used have different mechanisms in vertigo control and the effect of ITD is immediate while HDBH needs longer time to achieve decrease in vertigo spells (Albu et al., 2014). However, there are current treatment protocols demonstrating improved hearing and vertigo control when higher doses of IT steroids are used. Recent literature suggests the dose should be 24 mg/ml (McRackan et al., 2014). As previously stated, we were using a low concentration steroid dosing (4 mg/ml) and that may account for the difference in treatment outcomes.

We can conclude that in the lack of high doses of ITD, using the treatment protocol concentration, betahistine added to improved outcomes. As previously reported, there were no significantly effects on hearing levels and tinnitus scores with this combination (James, Burton, 2001, Itoh, Sakata, 1991, Shea, Ge, 1996, Garduno-Anaya et al., 2005, Silverstein, 1998, Barrs et al., 2001, Barrs, 2004, Boleas-Aguirre et al., 2008, Parnes et al., 1999, Casani et al., 2012). Despite these preliminary favorable results, a larger sample should support our initial results.

I.4. COCHLEO-VESTIBULAR INTERFERENCES: RESEARCH ON THE VESTIBULAR FUNCTION AND ITS IMPAIREMENT INDUCED BY COCHLEAR IMPLANTATION

Background

The cochlear implantation, a successful procedure to restore the hearing in deaf adults and children, is already widely used in the world. In the last years, the bilateral cochlear implantation became the standard especially in bilateral congenital profound deafness in children. Different pathological vestibular symptoms or damages were reported in cochlear implanted patients in post-operative period or later in time. Some of the children with profound congenital NSHL may present as well congenital vestibular impairment, due to the anatomical and embryological relation of the different parts of the inner ear. The prevalence of the vestibular dysfunction in children with NSHL ranges from 20% to 85% (Cushing et al., 2008, 2013, Shinjo et al., 2007). This variability is related to the different associated conditions and pathologies as: genetic non-syndromic or syndromic hearing loss (Usher, Jervell and Lange Nielsen, CHARGE, Waardenburg, Pendred, Goldenhar, DiGeorge), isolated malformations of the internal ear, the enlarged vestibular aqueduct (Wiener-Vacher et al., 2018), congenital citomegalovirus infection, ototoxicity of pharmaceutical substances (Gentamicin) which can lead to hearing loss and bilateral vestibulopathy (Huang, Bi, 2017, Lin et al., 2018, Strupp et al., 2016, Albernaz et al., 2019). As well, the anatomical reports between cochlear and vestibular spaces could prone the vestibular dysfunction due to cochlear implantation. Despite the increased interest for this topic in the last years, still there is a limited number of studies about vestibular possible consequences after cochlear implant surgery. Patients with hearing loss who underwent cochlear implantation can present symptomatic or asymptomatic vestibular damages earlier or later after the surgery. The vestibular permanent lesions could be acute, produced by surgical trauma or could be progressive due to local morphological changes made by the presence of the portelectrode in the inner ear (fibrosis related, ossification, basilar membrane distortion, endolymphatic hydrops). Besides histopathological findings in inner ear

of cochlear implanted patients, the vestibular permanent damages could be found by assessment of clinical vestibular status. The bilateral implantation is more and more indicated in children than unilateral implantation due to the important advantages increasing the life quality. One of the reported complications of CI surgery is the vestibular damage, which can be transient or permanent. A recent review confirms that the postoperative vestibular lesion's rate is highly variable, between 18% and 85% of the implanted children. It is also reported in the literature the vertigo induced by electrical stimulation through the portelectrode (Mangham, 1987, Brey et al., 1995, Huygen et al., 1995).

I.4.1. The influence of cochlear implantation on saccular function in hearing impaired children

Introduction

The occurrence of the vestibular deficiency in childhood, especially the bilateral one, leads to a chronic instability that will affect the child's motor and cognitive development. The prognosis is more severe if the vestibular deficit is present before the age of one year, because the child has not yet developed his walk and balance abilities (Kaga, 1999, Masuda, Kaga, 2014). In these cases can appear axial hypotonia, problems of spatial and body representation. Cognitive loss could be generated by errors in building the self-image through relationship with the others and the space (Borel et al., 2008, Brandt et al., 2005, Cioni et al., 1984). An important factor that may influence the preservation of both cochlear and vestibular neurosensory epithelium is the surgical approach. There are two ways to rich the intracochlear space: through the RW and by CO.

Main articles published in this field:

- **Romică Sebastian Cozma**, Maria Cristina Hera, Mihail Dan Cobzeanu, Raluca Olariu, Oana Roxana Bitere, Cristian Mârțu, Lucia Corina Dima-Cozma, Cristina Gena Dascălu, Mădălina Gabriela Georgescu, Violeta Necula, Luminița Mihaela Rădulescu. Saccular function evolution related to cochlear implantation in hearing impaired children). *Romanian Journal Of Morphology And Embryology.* 2020; 61(1):113–119 (IF=1,500).
- Cristina Hera, **Sebastian Cozma**, Luminița Rădulescu, Cristian Mârțu, Oana Bitere, Lucia Corina Dima-Cozma, Raluca Olariu, Mihail Dan Cobzeanu. Funcția otolitică la pacienții implantați cohlear. (Otolithic function in cochlear implanted patients). *ORL.ro.* 2018; 38(1): 25-27. ISSN 2067-6530
- Cristina Hera, **S. Cozma**, Oana Bitere, C. Mârțu, Luminița Rădulescu, Mihail Dan Cobzeanu. Importanța statusului vestibular la copilul cu indicație de implant cohlear. (Importance of vestibular status in children with a cochlear implant indication). *Rev. Med. Chir. Soc. Med. Iași*, nr 2/2018, supl. 1, 143-150; ISSN: 0048 - 7848.

Scientific contributions /Clinical implications:

- This was the first research in Romania and one of the few in the world that brings information about the impairment of vestibular sacular function in children induced by cochlear implantation. This function is essential for the development of walking in children, it must be preserved as much as possible. In this respect, the research results represent a strong argument for sequential bilateral implantation in young children.

The vestibular assessment before and after cochlear implantation has a very important role for very small children, since the normal motor development depends of the normal function of sensorial vestibular structures. For those children with vestibular impairment associated to the severe to profound hearing loss or vestibular damages induced by the cochlear implantation, the knowledge of the degree of the deficit is extremely important. This can lead to an appropriate undelayed vestibular rehabilitation treatment in order to favor the best recovery of the neuromotor skills based on the exceptional neural plasticity at this age.

Aim of the study

The rehabilitation of hearing loss by cochlear implantation should purpose to avoid to induce, if possible, any vestibular injury. To rich this objective, the vestibular status has to be assessed preoperatively. In practice, the cervical vestibular evoked myogenic potential (cVEMP) is the most used vestibular test in children, possible from 2–3 months of age. It is an objective, fast and non-invasive test, but some difficulties can appear when the child does not cooperate or in case of certain pathologies like neuropathies or muscular dystrophies.

Materials and methods

This prospective study enrolled 80 children (41 boys and 39 girls). The mean age at the implantation moment was 4.35 years. Thirty percent had a monolateral implantation, 50% had a bilateral sequential implantation and 20% a bilateral simultaneous one. The surgery was performed by the same surgeon for all cases. In order to respect the inner ear functional structures, the portelectrode insertion was done by atraumatic CO or by RW approach, depending also of the local anatomy.

After the surgery, a modified Stenvers radiography was done to verify the right position of the receiver-stimulator and intracochlear electrodes. The preoperative test protocol (T0) included the vestibular assessment of the saccular function by cVEMP. We performed a prior clinical examination of the ear by otomicroscopy and impedancemetry. The cVEMP was repeated postoperatively for each implanted ear in order to evaluate the preservation of saccular otolithic function. The test was scheduled at least three months after the surgery (T1) to avoid any transient vestibular deficit. For the cVEMP recordings, the sound stimulation was presented by air conduction through insert ear phones using tone burst with the following parameters: frequency of 500 Hz at the intensity of 100 decibels normal hearing level (dB nHL), duration of the stimulus of 2 ms, the rate of the stimulation 5.1 stimuli/s, the number of stimuli between 150 and 200 per run. We used the Eclipse evoked potentials device from Interacoustics, Denmark. Ipsilateral myogenic evoked potentials were recorded by placing the active electrode on the inferior third of the sternocleidomastoidian muscle (SCM), the ground electrode on the forehead, and the inverting electrodes on the retroauricular areas. For cochlear implanted patients, the sound processor was removed from the head before performing the cVEMP test.

Results

We analyzed first the preoperative saccular status in all 135 ears (defined as moment T0). In 75.6% of measurements, we obtained a cVEMP response, while in 24.4% of ears the saccular response was not present. After the CI surgery (defined as moment T1), in 53.3% of the implanted ears, the cervical vestibular myogenic potential was present, while 46.7% of implanted ears do not show any saccular response.

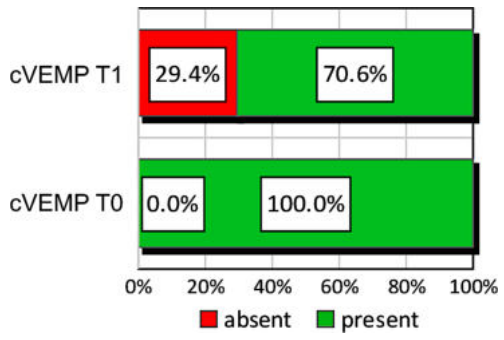


Fig. I.4-1.1. – Postoperative saccular function status (T1) in the group with preoperative present cVEMPs (T0) (n=102)

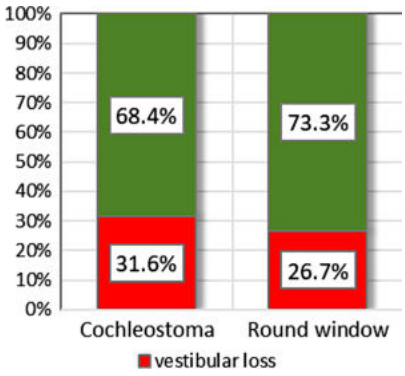


Fig. I.4-1.2– Postoperative saccular status (T1) in the group with preoperative present cVEMPs related to the surgical approach (n=102)

In order to highlight the real variation of the saccular function related to cochlear surgery, we should consider the saccular function variation only in the ears that in the preoperative moment had a present response for cVEMP. In consequence, in the group of 102 implanted ears with preoperative present cVEMPs, 70.6% preserved the saccular function after implantation, meanwhile 29.4% lost the vestibular potential. This variation may suggest the risk of injury that the surgical maneuvers for cochlear implantation and especially the intracochlear portelectrode insertion may have on the saccular neuroepithelium (Fig. I.4-1.1).

Figure I.4-1.2 presents the variation of the vestibular saccular function in the group of 102 ears (who had saccular response preoperative) considering the surgical approach for portelectrode insertion: CO versus RW. In the CO group, considering the ears with present preoperative saccular response (57 ears), we found that 68.42% preserved this response, while 31.58% lost the saccular potential. In the RW approach group, selected by the same principle (ears that had a preoperative normal cVEMP), 73.33% maintained the physiological saccular function and 26.67% present saccular areflexia.

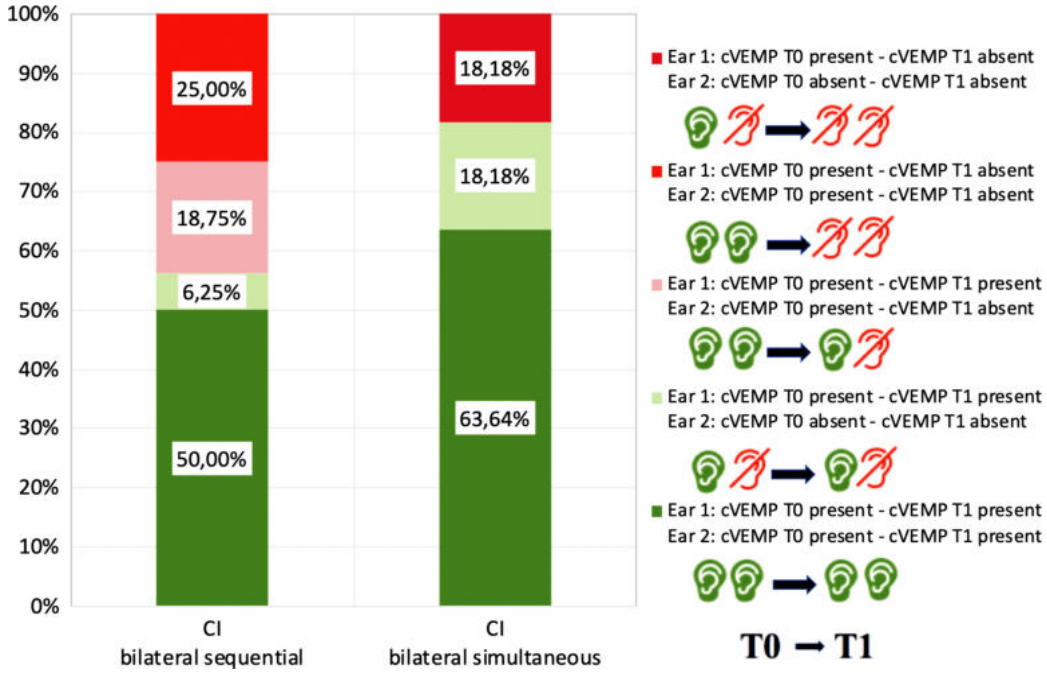


Fig. I.4-1.3. – Postoperative saccular status (T1) for bilateral sequential versus bilateral simultaneous cochlear implantation in children with at least one functional saccula at T0. CI: Cochlear implant; cVEMP: Cervical vestibular evoked myogenic potential.

We defined two subgroups including children with at least one functional saccula at T0 who were bilaterally implanted, but differ by the surgery time: sequential bilateral surgery versus simultaneous bilateral surgery. In the first group that had a bilateral sequential cochlear implantation, there are eight (25%) patients that have a bilateral saccular lost after the surgery. In the second group that had a bilateral simultaneous implantation, two (18.18%) patients present bilateral cVEMP loss (Fig. I.4-1.3).

Discussions

The saccula is the closest vestibular structure to the cochlea and have a major risk of lesion, as the anatomo- pathological studies have been shown (Handzel et al., 2006). The association of the diagnosed NSHL with the vestibular deficiency can suggest an inner ear global deficit. In this regard, in our group of patients, 24.4% of ears with profound hearing loss associate saccular areflexia. Cervical VEMP results vary with age, but some authors have used already this test in children with very good results, despite the fact that there are not valuable

guidelines published yet (Felipe, 2018, Picciotti et al., 2007, Chang et al., 2007, Sheykholeslami et al., 2005). In consequence, because there is no consensus protocol for a quantitative assessment of the parameters of the P1–N1 wave complex in children, we decided to analyze only the presence or the absence of cVEMP response for our study.

In our study, the bilateral saccular loss occurred in the group of bilateral sequential cochlear implantation, while in the group of simultaneous implantation, we have not identified any bilateral loss induced by the implantation. However, there are in this group some patients with bilateral saccular loss due to the unilateral damage produced by the cochlear implantation associated to a preoperative contralateral dysfunction. Analyzing the saccular status for the group of bilateral cochlear implantation depending on the strategy of simultaneous or sequential surgery, we observe the following: more than half of our patients have conserved the saccular function on both ears after the surgery (63.64% of simultaneous bilateral CI and 50% of the sequential bilateral CI); the unilateral injury induced by cochlear implantation in patients with preoperative bilateral normal function occurred in 18.75% for sequential surgery, while 18.18% lost their unique functional ear after the simultaneous surgery; the unilateral saccular function was maintained in 6.25% after the sequential implantation and in 18.18% after the simultaneous bilateral implantation; the complete bilateral loss of the saccular function induced by surgery was observed only in the sequential CI group for 25% of patients. The most important concern for bilateral vestibular loss refers to the simultaneous cochlear implantation.

In our study, at the preoperative moment (T0), the prevalence of the saccular areflexia was detected in 24.44%, while after the surgery (T1) was identified in 46.66% of the cases. We can conclude that the difference between these results indirectly indicates the group of patients that lost their saccular function for surgical reasons, the most important factor being the insertion approach. The RW insertion has the benefit that is not necessary to drill the basal turn of the cochlea. Using this approach might reduce the surgical trauma (Meli et al., 2016, Batuecas-Caletrio et al., 2015).

The portelectrode insertion by CO involves a risk of vestibular loss due to the drilling that may produce a mechanical and thermal aggression. There are discussions about the best CO place in order to assure the access for the insertion into the scala tympani and, in the same time, to avoid as much as possible the permanent vestibular lesions. In this regard and due to the ambiguity of the nomenclature for the topography of the CO, which makes difficult to understand certain anatomical notions, Badr et al. published some landmarks for the placement of the CO in a less traumatic manner in order to guarantee the insertion of the portelectrode into the scala tympani and to avoid as much as possible the vestibular damages. The authors sustain that the most secure place to perform the CO seems to be the intersection between B and C area (intermediate CO position – ICP) (Badr, 2018).

The vestibular impairment due to the cochlear implantation is much more important in infants, since they can benefit by bilateral devices even before walking acquisition. Jacot et al. report that the insertion through the RW could induce less vestibular impairment (10% of implanted children) than the CO insertion (Jacot et al., 2009), results confirmed also by Todt et al. (13% by RW versus 50% by CO) (Todt et al., 2008).

Reporting our findings related to the portelectrode insertion method, we found maintained saccular function in 73.3% of the cochlear implanted ears by RW surgical approach and in 68.42% ears by CO approach. These results suggest that the RW portelectrode insertion is the recommended strategy in order to avoid the saccular vestibular impairments we already shown in previous study carried out in adults (Cozma et al., 2018). The risk of permanent vestibular deficit with affected balance abilities and other clinical manifestations should be discussed with patient before surgery (Todt et al., 2008).Using minimally invasive surgical techniques and less traumatic devices, we can avoid the cochlear and vestibular lesions not only for the first cochlear implantation intervention, but also for the reimplantation purposes, even

these cases are not very frequent, as many studies have shown, the CI devices having a very good reliability (Rădulescu et al., 2013, Lane et al., 2020, Yeung et al., 2018).

Conclusions

In our group of cochlear implanted children with preoperative normal saccular function, the surgery was followed by a loss of saccular function in 29.4% of cases, which confirm the significant vestibular risk of the CI surgery in pediatric population. Anyway, the benefit of CI is undeniable, but the surgical method for the portelectrode insertion could be adapted, depending on the local anatomy, in the favor of the RW approach, our study emphasizing a smaller vestibular impairment due to the surgery (26.7%) comparing with the CO approach (31.6%). However, the RW insertion and the sequential bilateral implantation are strongly recommended as the probability to induce the simultaneous bilateral vestibular loss is significantly reduced.

I.4.2. Vestibular sensory functional status of cochlear implanted ears versus non-implanted ears in bilateral profound deaf adults

Introduction

As more and more patients are cochlear implanted every year, the number of patients exposed to vestibular damage risk increases. During the cochlear implantation surgery, the insertion of the electrode array may damage the vestibular peripheral receptor, as it is demonstrate by some histopatological studies (O'Connell et al., 2016). Handzel et al. show that in 59% of the implanted bones the cochlea was hydropic and in the majority of study bones the saccula was collapsed (Handzel et al., 2006). The mechanism could be represented by the portelectrode insertion process inducing a cochlear direct trauma, as well as: perilymphatic fistula, endolymphatic hydrops, intraoperative gusher, autoimmune reaction in inner ear caused by the presence of the electrode, local infectious contamination, vascular lesions (ischemic or hemorrhagic) or direct electric stimulation (Tien, Linthicum, 2002). In the last years, different authors present advantages and disadvantages of two possible inner ear approaches: cochleostomy (CO) and round window (RW) electrode insertion. The vestibular impairment prevalence due to cochlear implantation reported by different authors is highly variable, as well as its association with each insertion technique (Ibrahim et al., 2017).

Main articles published in this field:

- **Romică Sebastian Cozma**, Lucia Corina Dima-Cozma, Luminița Mihaela Rădulescu, Maria Cristina Hera, Cristian Mârțu, Raluca Olariu, Bogdan Mihail Cobzeanu, Oana Roxana Bitere, Mihail Dan Cobzeanu. Vestibular sensory functional status of cochlear implanted ears versus non-implanted ears in bilateral profound deaf adults. *Romanian Journal Of Morphology And Embryology.* 2018; 59(1): 105-112. (IF=1,500)

Scientific contributions /Clinical implications:

- This is the first article in Romania that investigates vestibular function in patients with cochlear implant, describes the incidence of vestibular impairment associated with deafness in Romanian patients and evaluates the functional implications of cochlear implantation on balance function.

For unilateral permanent vestibular impairment, medical treatment and vestibulary rehabilitation are efficient for vestibulary compensation in order to restore the patient's balance (Georgescu et al., 2012). If the cochlear implantation is performed on both ears and the vestibular peripheral system is bilaterally affected, the consequences on patient's balance could be very serious, especially in children (Krause et al., 2010). In some rare particular cases of deaf patients with associate vestibular and additional injuries (genetic rare diseases), the

vestibular assessment before the cochlear implant surgery could be very limited due to malformations of the ear or more complex, muscular deficits (oculomotor, cervical and facial) making impossible to record ocular and cervical vestibular evoked myogenic potentials or to perform vestibular caloric tests (Hînganu et al., 2017).

Aim of the research

The aim of our study was to evaluate the status of vestibular peripheral sensors in cochlear implanted ears versus non-implanted deaf ears in adults and to analyze a possible correlation of postoperatory vestibular sensory status with the type of electrode insertion approach: cochleostomy and round window.

Materials and Methods

In this retrospective cohort study, we included 27 adult patients (age range 16 to 73 years, with a mean of42.40 years) with bilateral profound acquired hearing loss, excepting meningitis, post-traumatic deafness or otospongiosis and without any known vestibular disease in history. Some of them underwent surgery for cochlear implant for both ears (12 patients), others for one ear (eight patients), and the rest were not implanted (seven patients). From this group of patients, we selected a subgroup of cochlear implanted patients (32 ears with a mean age of 41.71 years) and a second group of non-implanted patients (22 ears with a mean age of 42.95 years), without any otological surgery in the past. We included only patients that have complete cochlear insertion of the portelectrode and who underwent a complete vestibular sensorial battery assessment with interpretable results for all tests. The insertion type was through the round window in seven cases and cochleostomy in 25 cases.

The time between cochlear implant surgery and the vestibular examinations ranged from three to 22 months. Each patient was assessed for vestibular status of peripheral sensors using the same examination protocol including the following tests: clinical examination of the ear, tympanometry, bithermal air caloric test for horizontal semicircular canal, cervical and ocular vestibular evoked myogenic potentials (cVEMP, oVEMP). The caloric ear irrigation was performed by irrigating the external auditory canal with a flow of warm air at 50°C and cold air at 24ºC by Air Fx Caloric stimulator, Interacoustics, Denmark, for 60 seconds on each ear. The tests were performed according to British Audiology Society guidelines (British Society of Audiology, 2010). The saccular sensorial organ activity was measured by cVEMP and the utricular sensorial organ activity by oVEMP; the patient was lying down, stimulated by sound air conduction, tone burst at 500 Hz at 100 dB nHL (decibels above normal adult hearing level) through ear insert phones, 2 ms duration, 5.1 stim/s, between 120 and 200 sweeps per run (Eclipse evoked potentials machine from Interacoustics, Denmark. The parameters for P1–N1 complex of the obtained waves were analyzed for both cVEMP and oVEMP.

Results

All mentioned sensors were evaluated for all patients in study groups, non-implanted and cochlear implanted ears. If we consider as vestibular damaged each ear with at least one sensor affected by hyporeflexia or areflexia, the tests for peripheral sensors show vestibular impairment in our non-implanted deaf group in 11 ears (50% of cases) and for cochlear implanted group in 17 (53.12%) ears. The patients with round window insertion present a bigger percentage of ears with at least one sensor affected (57.14%) comparing with the cochleostomy group (52%). Both subgroups present a bigger percentage of vestibular damaged sensors comparing with non-implanted ears (Figure I.4-2.1). The normal vestibular function was considered if all tested sensors of an ear present normal functional parameters: 50% of non-implanted ears and 46.88% of cochlear implanted ears. The normal vestibular function was present in 48% for patients with electrode insertion by cochleostomy and 42.86% for those with round window insertion (Figure I.4-2.1).

The functional evaluation of lateral semicircular canal measured by caloric vestibular test showed that this sensor is the less affected one in cochlear implanted ears, presenting

normal function in 84.38% (27) ears. A hyporesponsiveness of the lateral canal has been found in 9.38% (three) ears and areflexia in 6.25% (two) ears. Ocular VEMP revealed that the utricule has been the most injured sensor in cochlear implanted ears (40.63%), as for the rest of 59.38% the utricular sensor has been found normal. In all implanted ears with utricular impairment, the oVEMP was not elicited, showing a total utricular lost in each case. In 65.63% of cochlear implanted cases (21 ears), we found a normal saccular function for cochlear implanted ears, elicited by cVEMP. The pathological saccular sensors have been found for 34.38% (11) ears, with hyporeflexia in 9.38% of cases (three ears) and saccular areflexia in 25% of implanted ears (eight ears). The most affected vestibular sensor in our cochlear implanted group was the utricle (40.63%), in all cases presenting areflexia. Areflexia was overall the most present damage for vestibular sensors in cochlear implanted ears. The results for lateral semicircular canal, saccular and utricular function are shown in Figure I.4-2.2.

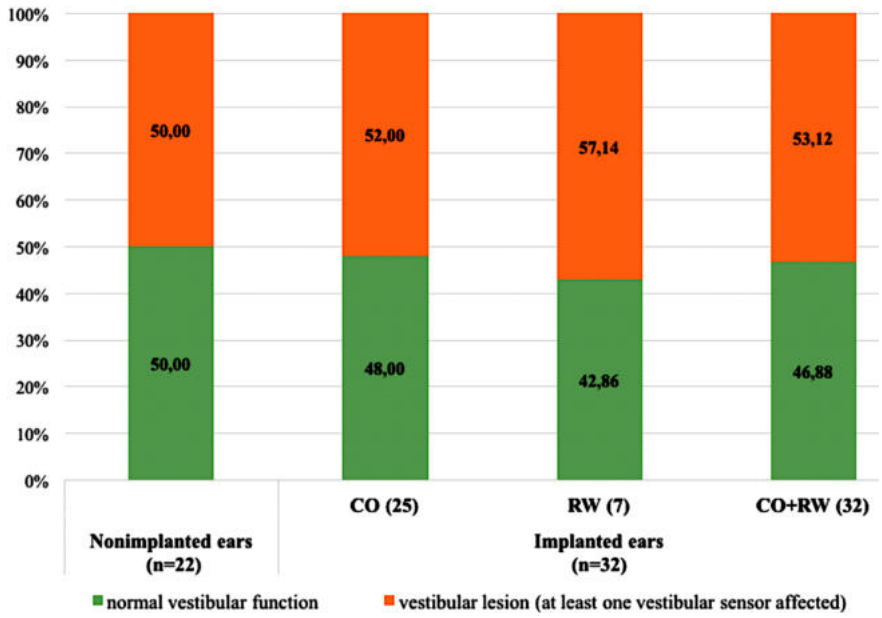


Figure I.4-2.1. – Vestibular function in non-implanted ears and in cochlear implanted ears with different portelectrode insertion: cochleostomy and round window (vestibular lesion of at least one sensor per ear). CO: Cochleostomy; RW: Round window.

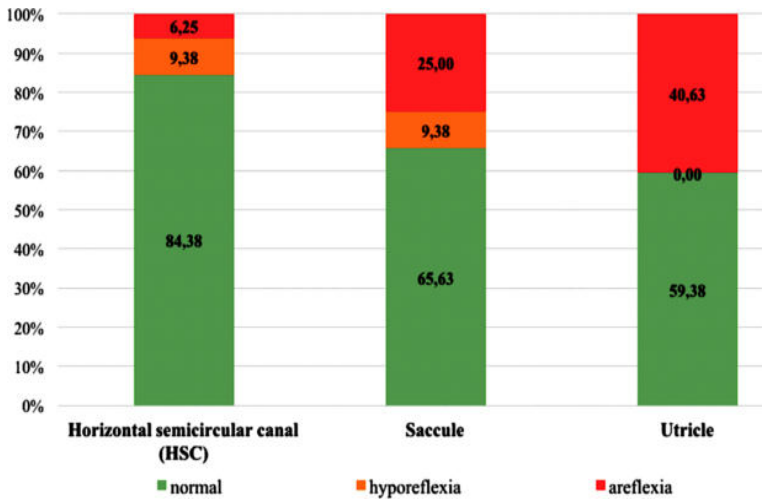


Figure I.4-2.2. – Vestibular sensorial status in cochlear implanted ears: hyporeflexia and areflexia of horizontal semicircular canal, saccule and utricle compared to postoperatively sensorial functional preservation (n=32).

The vestibular sensors could be differently influenced by different approaches for the insertion of cochlear implant's portelectrode. We analyzed the vestibular assessment results depending of the insertion methods: cochleostomy and round window approach. For semi-circular lateral canal, we found non-damaged cupularsensors in 88% for cochleostomy and 71.43% for round window technique. Hyporeflexia was the dominant consequence of cochlear implantation for horizontal canal (8% in cochleostomy and 14.29% in round window insertion) and areflexia was less important for cochleostomy (4%) and similar with hyporeflexia (14.29%) for round window approach. The normal saccular function was preserved significantly better in round window insertion (85.71%) than in cochleostomy cases (60%), which present 12% of hyporeflexia and 28% of areflexic saccular sensors. As mentioned above, the utricular sensors present only areflexia in cochlear implanted ears, for cochleostomy have been found a complete loss of the function in 44% of ears and for round window in 28.57% of ears. For our study subgroups of cochlear implanted ears, the round window approach preserved better the saccule and utricule and the cochleostomy was less traumatic only for horizontal semicircular canal (Figure I.4-2.3).

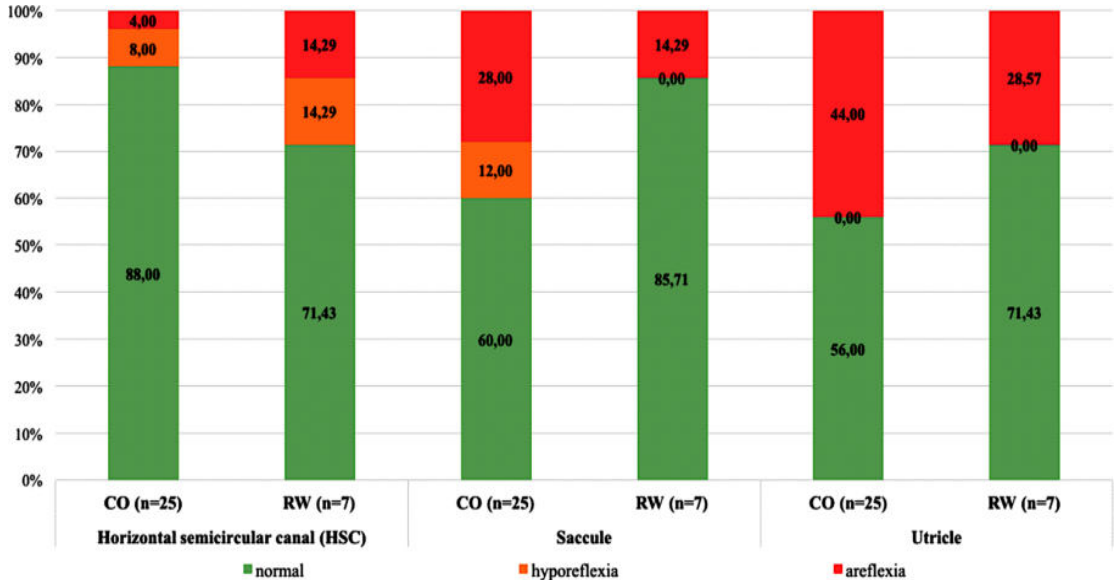


Figure I.4-2.3. – Comparison of vestibular sensorial status (normal function, hyporeflexia and areflexia) for horizontal semicircular canal, saccule and utricle related to cochleostomy and round window insertion approaches. CO: Cochleo- stomy; RW: Round window.

Considering the globally vestibular injury reported to all tested peripheral sensors of cochlear implanted ears depending of portelectrode insertion strategy, we found a better vestibular sensorial conservation for round window insertion which presents 76.19% normal sensors postoperatively, 4.76% hyporeflexia and 19.04% areflexia. For cochleostomy approach, we found 68% of normal vestibular sensors, 6.66% hyporeflexia and 25.33% areflexic sensors. Both hyporeflexia and areflexia presents increased percentages comparing with round window insertion.

Discussion

The vestibular assessment was made respecting a time delay for cochlear implanted ears of at least three months in order to avoid some transitory vestibular injuries after cochlear implantation. We considered that in the control group of deaf patients the prevalence of the vestibular dysfunction should be the same like in the selected study group, for many cases of hearing loss the etiology remaining unknown. Thus, the increased number of the injured vestibular sensors in cochlear implanted group was assumed to be a consequence of the surgery. In our study, the vestibular sensors of cochlear implanted ears were globally more affected by

the port-electrode insertion through the cochleostomy than through the round window. In the last years, many researchers published data showing the advantages of round window insertion which does not need to drill the basal turn of the cochlea reducing the surgical trauma (González-Navarro et al., 2015, Meli et al., 2016, Batuecas-Caletrio et al., 2015). Our results confirm the advantage of using round window insertion for a maximal conservation of the vestibular function. There are also studies showing that the results of vestibular tests were not significantly different before and after cochlear implant (CI) surgery between the cochleostomy and round window groups (Kluenter et al., 2010). The lateral semicircular canal seems to be the most respected sensor by the cochlear implant surgery for our patients, in over 84% of implanted ears the function was found normal. Batuecas–Caletrio et al. described by video head impulse test postoperative change in vestibular function in 30% of cochlear implanted ears and they suggest that round window approach should be recommended for less inner ear trauma (Batuecas-Caletrio et al., 2015) . In other study, Krause et al. showed a significant postoperatory worsening of the caloric response in 32% of patients (Krause et al., 2009)

Saccular sensors evaluated by cVEMP testing revealed a less altered function compared with utricular sensors and more injured related to horizontal semicircular canal. For the cochlear implanted affected ears, the saccular areflexia was significantly much more present than saccular hyporeflexia (25% vs. 9.38%). This conclusion confirms other author's results (Meli et al., 2016, Krause et al., 2009). The round window insertion way should be more secured for saccular sensors than the cochleostomy method (Batuecas-Caletrio et al., 2015).

For some monoaural cochlear implanted patients with utricular areflexia on the implanted ear, we found a normal utricular function on the contralateral ear. Thus, we could presume that for these patients at least the utricular sensors could be considered to be damaged by the cochlear implantation surgery. From our data, the round window insertion would be better tolerated by utricular sensors, which present a less important damage (28.57%) comparing to the cochleostomy (44%).

There are wide discrepancies in clinical results regarding the sensorial deficits found by different studies (Ibrahim et al., 2017). For lateral semicircular canal, the deficit was reported between 19% to 93%, while for saccular deficit, very rarely reported, the deficit widely varies between 21% and 100% in different studies (Huygen et al., 1995, Ito, 1998, Jin et al., 2006, Mangham, 1987, Szirmai et al., 2001, Todt et al., 2008, Nair et al., 2016, Abouzayd et al., 2017).

The vestibular sensorial status after cochlear implant is much more important for children than for adults, since they are nowadays implanted at a very early age, even before walking. Wiener-Vacher reports that the use of round window approach could induce a vestibular impairment in 10% of implanted children, close to results published by Todt et al. (13%) and significantly lower than 50% in children with cochleostomy. The round window insertion and the sequential bilateral implantation would be recommended in order to prevent the bilateral vestibular loss (Todt et al., 2008).

Conclusions

Cochlear implantation represents an important risk factor for injury of the peripheral vestibular receptors. Our study revealed significant vestibular changes on cochlear implanted ears vs. non-implanted deaf ears. We can affirm that in our implanted patients the global vestibular lesions were less important for round window approach compared with cochleostomy electrode insertion. Using minimally invasive surgical techniques, like round window insertion approach, and also less traumatic devices for inner ear, the conservation of vestibular sensory function will be improved in the advantage of cochlear implanted patient's balance.

SECTION II
Future projects in the professional, academic and scientific field

Perspectives in the professional activity

Because, within the ENT specialty, I chose to dedicate myself to the field of audiophonology and vestibology, my future projects in the professional plan are related to auditory and vestibular pathology, to providing medical care on this level for our patients, both adults and children, all the more as the service that I run is a reference in the country and the only one in the area of Moldova. Thus, my future projects involve the development of the audiology service to increase the addressability for patients with ENT disorders in the field of hearing, vestibular and speech disorders. The putting in practice of medical ideas and knowledge aquired from documentation and research represents a goal of itself in the professional perspective.

Deafness is a pathology that affects over 10% of a country's population, according to WHO communications, and the cost of unaddressed deafness is huge, exceeding the costs of possible interventions to eradicate deaf mutity. The moderate, severe and profound hearing loss led to a sensorial handicap, with major and complex impact for hearing-impaired person and also for his family. Hearing loss, due to a large number of deaf persons is recognized as a public health issue. In consequence, every country and society should adapt the health politics in order to offer health services covering the hearing screening, the diagnostic and the intervention for each deaf patient. The present assessment tools lead to the diagnosis of congenital deafness starting with the first days after birth (Johnson et al., 2005). These tests are noninvasive, easy to be used, and are highly available for usage as screening tools for deafness in maternities (Norton et al., 2000).

Since deafness continues to be the most common pathology present at birth, the collaboration of the ENT and Audiology services with the colleagues in Neonatology is extremely important for the successful management of these cases. As for us, we have been successfully having a traditional and collaborative relationship with neonatology for over 12 years now. Due to this successful model, the authorities understood the importance of the approach and supported the implementation of universal neonatal hearing screening throughout Romania in 2019.

As a future project, I propose to continue the development of the auditory screening program through several new directions:

- the creation of city and / or county screening retesting centers where the mothers can show up with their children for the follow-up stages of the mandatory protocol, given that the maternity hospitals can no longer receive children after the age of 1 month old;
- completing the protocol of universal maternity screening tests with auditory evoked potentials in order to avoid undetected auditory neuropathies, which can pass the acoustic otoemission test, but also having the advantage of immediate information on the probability of a diagnosis of deafness.

Different publications sustain that over 50% of children who are diagnosed with hearing loss in preschool and school screening are coming from the category who passed the screening tests after birth (Watkin & Baldwin, 2011).

Therefore, another future project is the development of the following stages of auditory screening: preschool and school screening, using a different methodology from that of neonatal screening, adapted to the age of the children.

Currently, there is a national registry of the RENSA deafness conducted at the same time as the national screening, but it is not yet operational. One of the future projects is the

mobilization of resources to activate this very useful registry in terms of managing this pathology on a national scale.

Future projects in the field of deafness treatment include collaboration with colleagues from the hospital, those from specialized clinics in the country, the ENT commission of the Ministry of Health and the National Health Insurance House in order to ensure access to its modern means to all of the patients.

As the national coordinator of the implantable hearing aid treatment program, I am considering initiating a consultation process with colleagues from cochlear implant centers to update the rules on the candidacy of patients (adults and children) for treatment with implantable hearing devices. It is known that throughout the country there are cases and situations of certain patients who cannot be enrolled in this national treatment program, even though their only medical option is cochlear implantation, and the adaptation of the rules to the medical reality must be done as soon as possible. I am also considering continuing efforts to upgrade the cochlear implant program, which should include a period of rehabilitation through speech therapy and hearing education at least for children with cochlear implants who also have prelingual deafness.

I will continue to work in the cochlear implant program for hearing loss treatment with my colleagues at the Rehabilitation Clinical Hospital, both by modernizing clinical diagnostic methods and by completing and diversifying methods for evaluating treatment outcomes.

The many internships that I have done in order to learn the fitting strategies of the implantable hearing devices are giving me the opportunity to adapt the working strategy with each different patient.

By developing healthcare for hearing-impaired patients, I am following for the future a few directions in the development of the audiology service:

- introduction in our services of electrocochleography for diagnosis and research in the field of auditory neuropathies;
- introduction in clinical practice of cortical auditory potentials for diagnosis, but also to assess the evolution after prosthesis or implantation;
- introduction of real ear measurements to evaluate the results of the hearing aid intervention;

Balance disorders and dizzying syndromes account for over 30% of the patients entering the family doctor's office, which indicates the need for vestibular diagnostic centers both in the emergency regime and in the chronic phase.

Regarding the services offered by CNAS for patients with vestibular problems, they do not cover the needs of diagnosis and treatment, while not being in agreement with the current clinical possibilities. Therefore, another proposal for the near future is to propose and support the updating of the package of diagnostic and treatment services for vestibular pathology.

The plans for the development of healthcare for vestibular patients follow several directions for the near future:

- introduction of vestibular evaluation by rotary tests;
- implementation of vestibular rehabilitation strategies for adult patients with vestibulopathies, but also for children with vestibular peripheral deficits;
- preparation through documentation, endowments and training of human resources of a new field of the future - the vestibular implant - in the case of patients with severe bilateral vestibulopathies;
- increasing the capacities to detect vestibular pathology in young children, with the potential for delay in locomotor development - organizing within the service a direction of vestibular rehabilitation in children.

Perspectives in the academic activity

Since my academic activity has so far been related to the teaching act, the passion to understand phenomenons and physiological and pathological processes and the desire to implement in medical practice the news in diagnosis and intervention in pathology from our specialty, I am stating that in my short-term and long-term future projects, these desideratums will always be present. Transmitting knowledge to students and residents is for me a way of being, it is a goal in itself of daily activities.

Fulfilling an older project - developing a manual for vestibular pathology in collaboration with the lecturers of the courses we have organized repeatedly, reflecting the clinical experience in the specialty, while using all of the information presented in the lectures during the postgraduate course – became an aim for the near future. The manual will treat the syndromes of vertigo and dizziness in an interdisciplinary manner, being a unique project in our country. Being an interdisciplinary approach and treating a very common pathology, the book will address ENT specialists, neurologists, cardiologists, family doctors, endocrinologists, ophthalmologists, psychiatrists.

The publication of course textbooks and practical papers for students of the Faculty of Medicine and Dentistry in French, series of courses which I am currently teaching, is another project for the near future.

One of the most important goals for the future is the collaboration with the management of our university regarding the resumption of studies, after 10 years, on the bachelor's degree in Audiology and Hearing Aid, a fairly advanced approach that the University of Medicine "Grigore T Popa" has already been preparing for over a year. This offer of university studies is extremely necessary, critically necessary as I would say, because in Romania there are no audiologists and audio-prosthetists, although there are extremely many hearing aids offices which have hired working staff that have no studies. This puts at risk the auditory rehabilitation of patients with such needs, especially young hearing-impaired children, whose development depends imperatively on a well-adapted prosthetic solution.

The development of international relations has been a goal for me in all of my work, being convinced that they could represent an engine of progress for our academic and scientific community, a source of inspiration for modernizing the means and methods of work in health care and also in education and in scientific activity. Thus, I plan to continue the interuniversity relations established with colleagues and universities in Rome, Lyon, Chisinau, Siena, but also the development of new relationships, in the near future projects being relations with universities in Canada (London), Turkey (Istanbul) and Germany . These new contacts are necessary, inclusively to the development of the education of audiology and hearing aids that I promote, in order to overcome the existing gaps. In Romania, education in this direction has been lacking, and experienced specialists from prestigious universities around the world can bring the impulse that we need.

Of course, I am considering the preparation of the new course directions and the elaboration of textbooks for the students of the new Audiology and Hearing Aids study direction, which will mean a concentrated effort together with the team from the ENT discipline.

In my academic development projects there is also the continuation of the annual organization of postgraduate courses which already have tradition: basic or advanced audiology courses, courses related to communication pathology and courses so far appreciated on the topics of vestibular pathology. Also, within the Romanian Society of Audiology and Communication Pathology, of which I am currently president, I will continue to promote the organization of working sessions, congresses and conferences that will continue the line already started a few years ago, promoting the interest of colleague specialists for: auditory screening

of deafness in the newborn child, treatment of deafness by cochlear implant, diagnosis and rehabilitation in vestibular disorders.

My presence in the International Bureau of Audio-Phonology (BIAP) currently as a member of the board of this organization gave me the opportunity to attract the organization of BIAP events in Bucharest for 2022 (the conference was scheduled for 2020, but was postponed this year because of the pandemic). Such a presence sensitizes the academic world and is a significant lobby for the importance of the field of audio-phonology, this field having been almost ignored for decades in Romania.

In order to fulfill the purpose of my academic activity, I will seek to attract young residents to clinical activities, especially in the audiology module I coordinate and instill a passion for this field, so that we can develop more diagnostic centers in the region and in the country. In fact, through my presence in the ENT Commission of the Ministry of Health, I supported and promoted a project to equip county hospitals with basic equipment for mandatory investigations in auditory and vestibular pathology. This project is not yet completed and it represents a concern for the near future.

Our academic mission to train human resources and promote the necessary facilities for modern health care can be accomplished by creating more specialized care services in the area around university centers, thus increasing the addressability of the population to quality health services.

In the medium term, I am considering the development of online medical education resources, on the university's e-learning platform, with the inclusion of various educational materials, courses, virtual clinical cases, specialized articles for course series that are annually distributed to me. Of course, the regular updating of these resources, as well as the materials used in the courses attended, is mandatory for maintaining a high-level teaching act, respected and sought after by students and residents.

Encouraging students and residents to participate in clinical trials and to present research results or clinical cases in specialized scientific events remains a concern for me and my team, as well as continuing to assist and support students attached to our concerns and who address us for the completion of their bachelor theses.

Future projects in the scientific activity

The scientific projects that I have approached and carried out so far were presented in the first part of the habilitation thesis. On the one hand, the realization of successful research is an invitation to continue them on other levels, and on the other hand pending projects, but which have the potential for scientific and clinical exploitation can be the focus of future development, along with young people working in our services or those who want to pursue doctoral studies.

In the presentation of the future plans for my research activity I will follow the main topics that I have exposed in the habilitation thesis and that I want to develop, of course together with other topics that will concern me in the future.

- ***Research on deafness and treatment with implantable hearing aids (cochlear implant and bone anchored hearing aids)***

Congenital hearing loss is the most common disease present at birth (1-3/1000 newborns). This problem is usually hidden at birth or in early childhood, being an invisible disability. Consequently the timely diagnosis can not be made than by actively detecting hearing impairment. The universal newborn hearing screening is the only method we can identify infants with possible hearing problems. Due to the neonatal hearing screening, the access to early diagnosis of deafness can be ensured. Hearing loss may be favored by the presence of risk

factors. Thus, it is known that deafness can occur both in children with and without risk factors present, neonatal hearing testing of children with risk factors for deafness is insufficient, and can exclude from diagnosis a significant number of children, representing, according to some statistics even over 50% of the newborn population (Watkin & Baldwin, 2011). The maturation of the auditory system after birth is achieved by myelination of the retrocochlear neural pathways and is dependent on sound stimulation, being achieved optimally when there are no auditory deficits (Moore & Linthicum, 2001, Moore et al., 1995). That is why children with hearing impairment have to be treated as early as possible with the new possibilities of deafness treatment either with powerful conventional digital hearing aids or with implantable prosthesis for middle ear (like BAHA - bone anchored hearing aid), for internal ear (cochlear implant) or for the eighth nerve (brainstem implants) (Davis, 1997).

In the direction of research related to diagnostic strategies in the pathology of the auditory system I will follow:

- researching the risk factors for deafness present in Romanian maternity hospitals, sensitizing the medical staff in neonatology and initiating, based on the research results, a process of decreasing their presence with effect on decreasing the prevalence of neonatal and perinatal deafness;
- continuation and development of the study of the field of auditory and vestibular evoked potentials;
- researching the optimization of diagnosis and intervention in the spectrum of auditory neuropathies, a very current topic worldwide; in this field, within the BIAP I lead the Technical Commission which has the task of elaborating the global guidelines for diagnosis and intervention in auditory neuropathies;
- research of the phenomena of auditory neural maturation in the deaf children who were implanted;
- research in the field of auditory perception and discrimination by participating in working groups within the European Federation of Audiology Societies;
- research of central auditory processing disorders by belonging to the APD working group (Auditory Processing Disorders) which aims to discover and implement new solutions in central auditory pathology and auditory processing disorders; I am a member of the working group within COST - AUDItOry PROcessing NETwork.
- we will continue the research on the RoVoIs audiological speech testing instrument, clinically validated on normal subjects; we have to develop the studies for the applicability of the tests in the case of patients of all ages with hearing loss. The project is developed on the basis of an interuniversity partnership with colleagues from other university centers in Romania.

The cochlear implant is a scientific concern continuously present in our team, the research directions in this field being multiple: from strategies for optimizing surgeries through minimally invasive surgery, to the development of products with minimally invasive characteristics, but also with the possibility of acoustic signal processing that brings as close as possible qualitatively the hearing of the implanted patient to the normal hearing. Also, the bilateral implantation in children offers us a window of opportunity for the study of the phenomenon of development of stereophonic hearing, of the possibilities of sound localization in space. In the future, I intend to:

- publish the results of a study conducted on this topic and which demonstrates in patients with binaural implant a recovery of localization skills similar to the normal hearing persons after a period of spontaneous reeducation of over 4 years;

- research in order to optimize cochlear implant programming strategies to increase the verbal-auditory performance of implanted deaf patients is another concern that will develop in the future, in some doctoral study projects;
- scientific studies justifying the updating of treatment indications with modern hearing implants;
- researching treatment opportunities by cochlear implantation of borderline cases.

Another scientific research project that I want to develop in the future in partnership with institutions in France and Switzerland refers to the study of auditory hypersensitivity, a pathological entity that has not been realy studied so far. More and more patients are accusing hyperacusis in the context of modern living conditions, but currently there are no diagnostic tools and no possibilities for intervention except for psychological counseling.

- ***Research on the diagnosis and treatment of vestibular pathology***

Vertigo and dizziness, after headache, are among the most frequent presenting symptoms in ENT, in neurology and internal medicine clinics. A survey of over 30,000 persons showed that the prevalence of vertigo lies around 17% and rises up to 39% in those over 80 years of age (Davis, Moorjani, 2003). Vertigo and dizziness are not a unique disease entity. A large number of multisensory and sensoriomotor syndromes of various aetiologies and pathogenesis are considered under this name. The body balance can be maintain only by combined visual, somatosensory and vestibular inputs. Various dysfunction in one of these channels may lead to vertigo and imbalance (Nasher, 1997). A common perspective of ENT doctors, neurologists, and general medicine physicians is needed for a better diagnosis and treatment of vertigo and dizziness patients.

In case of bilateral vestibular deficiency the patients have a real difficulty to perform daily activities. The occurrence of the vestibular deficiency in childhood, especially the bilateral one, leads to a chronic instability that will affect the child's motor and cognitive development. If the vestibular deficit is present before the age of one year, the prognosis is more severe because the child has not yet developed his walk and balance abilities (Kaga, 1999, Masuda, Kaga, 2014).

In the light of the arguments presented above, research projects in this direction will include:

- studies for the development of an early vestibular diagnostic methodology, because currently all congenital or perinatal acquired vestibular diseases remain unidentified, and most are interpreted as specific neurological or neuro-motor pathology and treated inadequately;
- research in order to implement vestibular rehabilitation programs for young children;
- studies for establishing the optimal working methodology in order to obtain the compensation phenomenon in peripheral vestibulopathies in adults within the vestibular rehabilitation programs;
- research in the field of Meniere's disease, based on a rich database and an important number of patients diagnosed in our service;
- because in the current practice we identify many female patients with endocrinological disorders that accuse balance disturbances, the desire to initiate a new research was born, regarding the possible association or determination of vestibular effects by thyroid pathology.

- ***Research on the interaction of deafness treatment through auditory implants with vestibular function***

The cochlear implantation is already a successful procedure to restore the hearing in deaf adults and children, widely spread in the world. Nowadays, the bilateral cochlear

implantation became a standard intervention for children with bilateral congenital profound deafness.

The vestibular dysfunction in children with neuro-sensorial hearing loss has a prevalence between 20% and 85% (Cushing et al., 2008, 2013, Shinjo et al., 2007). In the same time, we know that one of the reported complications of CI surgery is the vestibular damage, which can be transient or permanent. Consequently, the vestibular impairment induced by cochlear implantation in very small deaf children will affect the balance and walking learning process. If the damage is bilateral, installed in early childhood, the children has a poor prognosis for the psychomotor and cognitive development.

A recent review confirms that the postoperative vestibular lesion's rate is highly variable, between 18% and 85% of the implanted children. By the cochlear implantation surgery, the electrode array's insertion could damage the vestibular peripheral receptor (O'Connell et al., 2016).

In the next period, in the medium and long term I will focus on the following topics in the intricate pathology of the inner ear:

- continuing research on cochlear-vestibular interactions in patients with deafness who benefit from cochlear implant, in the light of new evidences related to possible vestibular lesions induced by implantation in young children, with consequences on the development of walking in early childhood. The research envisages the elaboration of intervention protocols regarding the cochlear implantation in the deaf child before the development of gait, which can preserve the vestibular reserves, without compromising the audio-verbal development;
- a new direction of research that I intend to open is the vestibular implant for the rehabilitation of balance in patients with bilateral vestibular areflexia, who are unable to walk without support. This type of implant is at the beginning of its existence, having not yet entered in clinical practice. For our cochlear implant center, this would be a research topic for which we have human and technical capabilities and which would provide an advance of academic and professional development in terms of applied research results;
- the appearance and clinical use of the vestibular implant will generate, after all expectations, a problem similar to the current cochlear implant, namely the possible impairment of hearing by aggression of the inner ear, a hypothesis that can generate a new direction of research;
- continuing research on vestibular status in children implanted simultaneously and sequentially, using more tools to quantify vestibular function compared to studies so far.

In the development of the research projects that I have proposed, on already established topics or on new topics, I have in mind:

- attracting residents and doctoral students in the research activity;
- participating in grant competitions to sustain our research ideas in our fields of interest;
- developing the material base that would offer us new possibilities, usable in the field of research;
- cooperation with other services and institutions in the country and abroad, in order to carry out interdisciplinary projects.

In conclusion, my future research activity will focus mainly on the continuation of the study directions in which I have gained experience over the past 22 years, as well as on the initiation of new study and research directions in the field of ENT. The ideas expressed above will give rise to research programs funded according to the priorities and opportunities that I, together with the team I work with, will identify.

SECTION III

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