GRIGORE T. POPA UNIVERSITY OF
MEDICINE AND PHARMACY IASI

# HABILITATION THESIS

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**Associate Professor**

**2020**

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## NEUROSURGICAL CHALLENGES: FROM SURGICAL NEUROANATOMY TO SURGICAL INTERDISCIPLINARITY

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# Contents

# Summary

This habilitation thesis is a synthesis of my scientific, professional and academic activity that I have carried out after PhD thesis, in 2001. This habilitation thesis is structured in three sections divided into chapters and sub-chapters, as follows:

**Section I** consists in a summary of my scientific research activity during the postdoctoral period.

**Chapter 1** reviews my scientific, professional and academic activity over the 19 years since I have obtained the title of doctor in medicine.

**Chapter 2** discusses the pathology of brain tumors, pathology that is permanently dynamic not only because the classification of brain tumors is continuously changing due to introducing immunologic and genetics criteria, but also because of the fast development of technologies that can contribute to the decrease of morbidity, as well as improving the quality of life for diagnosed patients and those who have undergone surgery for brain tumors. Unfortunately, the incidence of brain tumors is continuously rising for all age groups, which has determined me to further the studies regarding factors involved in brain tumor occurrence, as well as factors involved in the prognosis of these tumors. In this sense, extranevraxial tumors have been studied, particularly intracranial meningiomas, respectively the particularities related to the changes of neighboring anatomical structures and their prognosis, the importance of demographic factors when it comes to the development of meningiomas, the possibility of this tumor becoming malignant, the importance of environmental factors and especially of the role of radioactivity in the occurrence and evolution of this type of intracranial tumor. Last but not least, I have studied prognosis factors of intracranial meningiomas correlated to neuroimaging factors, studies conducted in multidisciplinary teams. I have also studied primary intracranial tumors, being interested in their rapid and accurate diagnosis through minimally invasive techniques and efficient collaboration with the pathologist team. I was also interested in the study of secondary brain tumors, respectively of brain metastasis and especially of intracranial metastasis with rare localizations.

**Chapter 3** represents a study on brain and spinal cord trauma. Brain injuries represent, according to WHO statistics, the second cause of mortality worldwide and Romania deals with an increasing number of victims who suffer due to car accidents. I have been concerned by the possibility of improving the treatment and the health care given to patients, in order to reduce death rates, but also post-trauma morbidity. For this purpose, I have participated in a retrospective study, conducted in multiple centers, on evaluating the effects of Cerebrolysin in brain injuries, and I have also introduced the method of invasive intracranial pressure measurement for patients with brain injuries to the Neurosurgery Clinic of Iasi. These matters have been reported in specialized articles. Also regarding head injuries, I was interested in the study of brain trauma with a focus on neighboring anatomical structures, especially of the orbit, which has been reported in articles published in ISI journals, as well as in BDI journals. Regarding spinal cord injuries, I was interested in particular aspects of their pathophysiology, but also in rare cases of spinal cord injuries.

**Chapter 4** is dedicated to interdisciplinary. This chapter presents my interest in the study of pathology of the head, neurocranium and viscerocranium, for the complete understanding of neurosurgery. Understanding these aspects is essential for the minimally invasive approach for the skull base, respectively of the endoscopic endonasal transsphenoidal approach. For this purpose I

have conducted studies on the sellar and parasellar regions, on the optic chiasma, and on intraorbital and rhinosinusal tumors. This has given me the possibility to be part of multidisciplinary teams who have handled the treated of lesions located at the base of the skull, meaning: ophthalmologists, cranio-maxillofacial surgeons, ENT-specialists and plastic and reconstructive surgeons. On account of this collaboration, I was able to draft articles published in ISI and BDI journals. The experienced gained this way has offered me the possibility to be initiated and to improve in the minimally invasive approach to the skull base, meaning the transsphenoidal endoscopy. Studies regarding neurosurgical anatomy and neuroanatomy are also presented in this chapter, being considered necessary for the understanding of complex surgical approaches, for the planning and the surgical risks.

**Chapter 5** presents my interested in the interference of neurosurgery with other sciences that make up the neuroscience. I have discussed the collaboration with neurologists and neuroradiologists in establishing the diagnosis and treatment that can be performed in a team. I have studied the psychological implications of the personnel performing their activity in the neurosurgery services, the stress that the neurosurgeons are subjected to during neurosurgical interventions, the inter-human relationships in the medical communities. Last but not least, I was interested in the iconodiagnostic topic that I consider important for educational use for students and residents. All these studies have been reported in articles published in ISI journals and which have summarized in this last chapter.

**Section II** presents the development directions I propose for the future for the scientific, professional, and academic activity.

Regarding the scientific activity, I will consider the following areas: minimally invasive neurosurgery, the neurosurgical treatment of the diseases of the extrapyramidal system and of mental disorders, as well as head injuries. Specifically, I am considering as research topics the deep brain stimulation in psychic disorders, the role of the hypothalamo-pituitary axis in the evolution and treatment of severe head injuries and minimally invasive techniques in the surgery of epilepsy.

Regarding the professional activity, I aim to perfect the minimally invasive techniques in which I have been initiated.

For the academic activity, I aim to implement new learning techniques for students and residents and the permanently improve the curriculum in the neurosurgery discipline.

**Section III** consist of bibliographical references.

# Rezumat

Teza de abilitare este o sinteza a activității mele stiințifice, profesionale și academice, activitate pe care am desfășurat-o după obținerea titlului de doctor în științe medicale din anul 2001. Teza de abilitare este structurată în trei secțiuni împărțite în capitole și subcapitole, după cum urmează:

**Secțiunea I** este constituită dintr-un sumar al activității mele științifice și de cercetare desfășurate în perioada postdoctorală.

**Capitolul 1** face o trecere în revistă a activității mele științifice, profesionale și academice pe parcursul celor 19 ani de la obținerea titlului de doctor în științe medicale.

**Capitolul 2** pune în discuție patologia tumorală cranio-cerebrală, patologie în permanentă dinamică atât prin continua schimbare a clasificărilor tumorilor cerebrale datorită introducerii criteriilor imunologice și genetice dar și prin dezvoltarea rapidă a tehnologiilor care pot contribui la reducerea morbidității și mortalității postoperatorii dar și la calitatea vieții pacienților diagnosticați și operați pentru tumori cerebrale. Din păcate incidența tumorilor cerebrale este în continuă creștere pentru toate grupele de vârstă, fapt ce m-a determinat să aprofundez studiul în ceea ce privește factorii implicați în dezvoltarea tumorilor cerebrale dar și factorii care pot fi implicați în prognosticul acestor tumori. Sunt studiate tumorile extranevraxiale, în speță meningioamele intracraniene, respectiv particularitățile legate de modificările structurilor anatomice de vecinătate și prognosticul lor, importanța factorilor demografici în dezvoltarea meningioamelor, posibilitatea de malignizare a acestor tumori, importanța factorilor de mediu și în special rolul radioactivității în dezvoltarea și evoluția acestor tumori. Nu în cele din urmă am studiat factori de prognostic ai meningioamelor intracraniene corelați cu aspecte neuroimagistice, studii efectuate în echipe multidisciplinare. De asemenea, am studiat tumorile primare intracerebrale, fiind interesată de diagnosticul rapid și precis al acestora prin tehnici minim invazive și printr-o colaborare efecientă cu echipa de anatomopatologi. Am fost interesată și de studiul tumorilor cerebrale secundare, respectiv al metastazelor cerebrale, și în special al metastazelor intracraniene cu localizări rare.

**Capitolul 3** este reprezentat de studiul traumatismelor cranio-cerebrale si al traumatismelor vertebro-medulare. Politraumatismele cu componentă cranio-cerebrală reprezintă, conform statisticilor OMS a doua cauza de mortalitate la nivel mondial iar în România sunt tot mai multe victime datorate accidentelor rutiere. Am fost preocupată de posibilitatea de îmbunătățire a tratamentului și a îngrijirilor acestor pacienți, cu scopul de a reduce rata mortalității dar și a morbidității pottraumatice. În acest sens, am participat la un studiu retrospectiv multicentric pentru a evalua efectul Cerebrolysin-ului în traumatismele cranio-cerebrale și de asemenea, am introdus în Clinica de Neurochirurgie Iași, măsurarea invazivă a presiunii intracraniene la pacienții cu traumatisme cranio-cerebrale. Aceste lucruri s-au materializat în articole de specialitate.Tot în sfera traumatismelor cranio-cerebrale am fost preocupată de studiul traumatismelor cranio-cerebrale cu interesarea structurilor anatomice de vecinătate și în special a orbitei, fapt ce s-a concretizat în publicarea unor articole în reviste cotate ISI sau BDI. În cazul traumatismelor vertebro-medulare am fost interesată de aspectele particulare ale fiziopatologiei acestora, dar și de cazurile rare.

**Capitolul 4** este dedicat interdisciplinarității. În acest capitol am prezentat interesul meu pentru studiul în ansamblu a patologiei extremității cefalice, neuro- și viscerocraniului și înțelegerii

depline a actului neurochirurgical. Întelegerea acestor aspecte este definitorie în abordarea minim invazivă a bazei craniului, respectiv tehnica endoscopică endonazală transsfenoidală. În acest sens am realizat studii asupra regiunii selare și paraselare, a chiasmei optice, a tumorilor intraorbitare și a celor rino-sinusale. Acest lucru mi-a oferit posibilitatea de a face parte din echipe multidisciplinare care au efectuat tratamentul leziunilor situate la nivelul bazei craniului, respectiv: oftalmologi, chirurgi maxilo-faciali, ORL-iști, sau chirurgi plasticieni. În urma acestor colaborări am putut elabora articole publicate în reviste cotate ISI și BDI. Datorită experienței dobândite în acest fel am avut posibilitatea să mă inițiez și să mă perfecționez în tehnica minim invazivă de abordare a bazei craniului, endoscopia transsfenoidală. În cadrul aceluași capitol sunt prezentate și studiile legate de anatomia neurochirurgicală și neuroanatomie, studii necesare pentru înțelegerea abordurilor neurochirurgicale complexe, pentru stabilirea planning-ului și a riscurilor operatorii.

**Capitolul 5** prezintă interesul meu legat de interferența neurochirurgiei cu alte științe care intră în alcătuirea neuroștiințelor. Am luat în discuție colaborarea cu medicii neurologi și neuroradiologi în stabilirea diagnosticului și a tratamentului care se poate efectua în echipă. Am urmărit implicațiile psihologice ale personalului care își desfășoara activitatea în serviciile de neurochirurgie, stress-ul la care sunt supuși neurochirurgii în timpul intervențiilor neurochirurgicale, precum și relațiile inter-umane din colectivitățile medicale. Nu în cele din urmă am fost interesată de *iconodiagnostic*, o temă pe care o consider importantă pentru utilizarea în scop didactic, atât pentru studenți cât și pentru medicii rezidenți. Toate aceste studii s-au materializat în articole publicate în reviste cotate ISI sau BDI, articole care sunt sintetizate în acest ultim capitol.

**Sectiunea II** prezintă direcțiile de dezvoltare pe care mi le propun pentru viitor în ceea ce privește activitatatea mea științifică, profesională și academică.

Legat de activitatea științifică, voi avea în vedere următoarele domenii: neurochirurgia minim invazivă, tratamentul neurochirurgical al bolilor sistemului extrapiramidal și al afecțiunilor psihice, precum și traumatologia cranio-cerebrală. Concrect, îmi propun ca și teme de cercetare: (1) stimularea cerebrală profundă în afecțiunile psihice, (2) evaluarea rolului axului hipotalamo-hipofizar în evoluția și tratamentul traumatismelor cranio-cerebrale grave, precum și (3) dezvoltarea tehnicilor minim invazive în tratamentul chirurgical al epilepsiei.

Ca și activitate profesională voi avea ca scop perfecționarea tehnicilor minim invazive în care m-am inițiat de-a lungul timpului.

Pentru activitatea didactică voi avea ca scop implementarea de tehnici noi de invățare pentru studenți și medicii rezidenți și permanenta îmbunătățire a curriculei din cadrul Disciplinei de Neurochirurgie.

**Secțiunea III** este constituită din referințele bibliografice.

# Section I – Scientific, professional and academic achievements

## I.1.Introduction

This habilitation thesis reviews the academic, scientific and professional activity that I have conducted in over 30 years since I have defended my doctoral thesis, presenting it great details.

My professional career started in December 1990 as a registrar at the "Cuza Voda" Maternity of Iasi. That same month, I obtained a Junior Assistent position through the exam, within the Discipline of Neurosurgery at the Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, which marked the beginning of my teaching career. In 1993, I obtained the title of Assistant Professor for the same discipline, moving on to Senior Lecturer in 2006 and Associate Professor in 2019. In 1994, I was admitted as a doctoral student, starting my studies under the coordination of Prof. Mihai Rusu. My doctoral thesis has the title "Anterior communicating artery aneurysms", consisting in a retrospective study of 160 cases of anterior communicating artery aneurysms, which has established a prognostic algorithm for patients diagnosed with this pathology.

The public defense of the doctoral thesis was held on March 20, 2000, acknowledging me as a Doctor in medicine by the Order of the Minister of National Education of June 5, 2001 for the diploma Series B No. 0004604.

In 1991, I started my professional training in the field of Neurosurgery, being named specialist in neurosurgery by the Order of the Minister of Health no.3951/June 5, 1996 and then Ph.D. by the Order of the Minister of Health and Family no. 538/7 August, 2001. To complete my training, I attended practical training courses at the Neurosurgery Clinic of the "Bagdasar Arseni" Hospital of Bucharest, "Vlad Voiculescu" Cerebrovascular Disease Institute of Bucharest, Neurosurgery Clinic of the "Cavale Blanche Brest France" Hospital (A.F.S.A. November1998-April 1999). Between 1998 and 2001, I attended the neurosurgery courses organized by the European Association of Neurosurgery (EANS).

My postdoctoral evolution developed in the following areas: scientific, represented by clinical research, professional, represented by continuous improvement of knowledge and medical practice, and academic, teaching students and resident doctors at the "Grigore T. Popa" University of Medicine and Pharmacy Iasi.

Regarding my scientific and research activity, I participated as a member of the research grants awarded be means of competition:

1. Autologous neural tissue transplantation of olfactory mucosa and stem cells in the treatment of spinal cord injuries in dogs. "Grigore T. Popa" University of Medicine and Pharmacy of Iasi, University of Agricultural Sciences and Veterinary Medicine of Cluj Napoca, CNCSIS 599, contract PN II62-085 / 2008, University of Agricultural Sciences and Veterinary Medicine of Iași, "Prof. Dr. N. Oblu" Emergency Clinical Hospital Iași, Strong collaboration agreement Project no. 62-85. http://www.uaiasi.ro/PN2/BIONEURO/ro/

2. Stimulating the biointegration of craniospinal implants by coating with bioactive multilayer structures (Acronym: Biostim), contract no.71-110/18.09.2007. Program 4: partnerships in priority fields, Department of Research & - Materials, processes and innovative products.

During the clinical research, I participated in a retrospective, multicenter study on the effect

of Cerebrolysin in brain and spinal cord injuries, trial coordinated by Prof. Dafin Muresan, PhD, from the "Iuliu Haţeganu" University of Medicine and Pharmacy of Cluj-Napoca and funded by EbewePharma.

My scientific activity is objectified in 38 articles, 25 articles published as main author and 13 articles as co-author in ISI journals, journals with high impact factor: Lancet Oncology (IF= 35,386), International Journal of Molecular Sciences (IF=4,183), CNS&Neurological Disorders – Drug Targets (IF=2,761), World Neurosurgery (IF=1,723), Anatomical Science International (IF=1,566), Childs Nervous System (IF=1,327), Medical Hypotheses (IF=1.322), European Neurology (IF=1,235), 70 articles in BDI journals, and Hirsch index = 7.

At the same time, I contributed as author of chapters or co-author in the drafting of neurosurgical treaties and guides for neurosurgical and surgical practice:

1. PRINCIPLES OF NEUROLOGICAL SURGERY, editors: Richard G. Ellenbogen, Laligam N. Sekhar, Neil D. Kitchen, coordinator of the Romanian language edition Ioan Stefan Florian, editors of the Romanian version: Mihaela Dana Turliuc, chapters 15, 40, Publisher: Hipocrate, 2019, ISBN 978-606-94576-2-7, 886 pages.

2. SURGERY TREATY, 2nd EDITION, VI NEUROSCURGERY , edited by Irinel Popescu and Constantin Ciuce, Coordinators Ioan Stefan Florian, Ion Poeata. Turliuc Dana-Mihaela (author), 4 chapters: Vascularization of the brain, pp. 358-361, Dural arterial-venous fistulae, pp. 415-418, Cerebral tuberculosis, pp. 660-663, Tumors of the peripheral nerves, pp. 784-787. Publisher: Academia Română, 2014, ISBN 978-973-27-2445-3, 823 pages.

3. SURGERY TREATY, volume 2, under the coordination of Alexandru Vlad Ciurea. Dana Mihaela Turliuc (author), 1 chapter: History of Neurosurgery: Prof. Mihai Rusu, pp 77-80, Publisher: Medicala, 2011, ISBN 978-973-39- 0720-6.

4. INTEGRATIVE MODULE FOR THE STUDY OF THE BRAIN – TUMORAL PATHOLOGY OF MORFO-FUNCTIONAL AREAS, authors: Doina Azoicăi, Constantin Vladimir Buragă, Irina Draga Căruntu, Manuela Ciocoiu, Daniela Cristina Dumitriu, Daniela Druguş, Laura Gheucă Solovăstru, Danisia Haba, Bogdan Iliescu, Beatrice Gabriela Ioan, Irina Oana Moisei Constantinescu, Florin Dumitru Petrariu, Ovidiu Rusalim Petriş, Anca Sava, Dragomir Nicolae Şerban, Ionela Lăcrămioara Şerban, Dana Mihaela Turliuc (author), Şerban Turliuc, Traian Ţăranu, Publisher: "Grigore T. Popa" Iasi, ISBN 978-606-544-326-6, 396 pages.

5. GUIDE TO OPHTHALMOLOGICAL PATHOLOGY. DISEASES OF THE EYELID AND CONJUNCTIVE, authors: Anca Sava, Claudia Florida Costea, Gabriela Florenţa Dumitrescu. Coautori: Gabriela Dimitriu, Magda Broşteanu, Camelia Tamaş, Dana Turliuc (co-author), Irina Iuliana Costache, Cătălin Buzdugă, Alexandru Cărăuleanu, Andrei Cucu. Publisher: Academia de Stiinte a Republicii Moldova, 2015, ISBN 978-9975-85-007-0, 427 pages.

6. FUNDAMENTAL SURGICAL ABILITIES. STUDY GUIDE, PROTOCOLS, ASSESSMENTS, authors: Nicolae Ghețu, Ionuț Huțanu, Mihaela Perțea, Ovidiu Petriș, Vladimir Poroch, Paul-Dan Sîrbu, Camelia Tamaș, Dana Mihaela Turliuc (author), Adrian Bodescu, Corneliu-George Coman, Gabriel Vlad Necula, Alexandru Mihai, Dan-Cristian Moraru, Ștefan Morărașu, Vlad Pieptu, Victoria Streinu, Rareș Șova, Athens Florina Triupa, Răzvan Tudor. 3 chapters: Stage 1. Reception, transfer and positioning of the surgical patient, p.3-39, Stage 3. Preparation of patients for major surgery, p.163-170, Stage 7. Reception, transfer and positioning of the surgical patient, p.553 -

557. Publisher: "Grigore T. Popa" Iasi, 2014, ISBN 978-606-544-272-6, 647 pages.

7. CURRENT TECHNIQUES IN NEUROSURGERY, volume 1, Dana Mihaela Turliuc (co-author), 5 chapters: 3.2 Discovery of the brachial, supraclavicular, infraclavicular and axillary plexus, p.58-68, 3.4. The approach of the ventricular system, p.76-80, 3.5. Microsurgical reconstruction of the superior longitudinal sinus, p.81-87, 3.6. Ventriculo-peritoneal and ventriculo-atrial drainage, p.88-97, 3.13. Myelomeningocele and lumbar meningocele, p.152-162, Publisher: Statur Bucharest, 2003, 226 pages.

Regarding the professional activity, I have been concerned with learning and perfecting modern techniques of neurosurgery, especially the minimally invasive techniques. In this sense, I attended advanced courses in microsurgical techniques, endoscopy of the skull base and neuroendoscopy, as well as minimally invasive techniques in the surgical treatment of the diseases of the extrapyramidal system, as follows:

- Deep Brain Stimulation for Movement Disorders course. Practical Training for Neurologists and Neurosurgeons Nov 2018 and May 2015, Olomouc, Czech Republic.
- Course – Basic principles of Neuroendoscopy, Dec 2012 and April 2002, Discipline of Neurosurgery at the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca.
- Transphenoidal endonasal endoscopy internship Foch Hospital of Paris, France, March 2012, (non-remuneration internship contract N 6741735PO8A002).
- La therapie multimodale dans les lesions vasculaires cerebrales Course, April 2006, Iasi.
- Certificate on vascular microsurgery, March 2003, "Vlad Voiculescu" Cerebrovascular Disease Institute of Bucharest.

During the postdoctoral period (2002-2019), I performed more than 2400 neurosurgical interventions as the main surgeon, interventions concerning the entire neurosurgical pathology but also in collaboration with related specialties: ophthalmology, otorhinolaryngology, oral and maxillofacial surgery, plastic and reconstructive surgery and thoracic surgery.

The academic activity consisted in teaching students and residents in neurosurgery, as well as in other specialties, coordinating their license thesis, guiding students in scientific activities, and organizing workshops for residents and specialists:

- Joint Symposium on Neuronavigation & Neuroendoscopy with Hands-on Workshop, Iasi, 2014
- The II$^{nd}$ Joint Symposium on Neuronavigation & Neuroendoscopy with Hands-on Workshop and Pediatric Neurosurgery Course, Iasi 2015

In the same context I participated in educational programs for students and doctors:

1. TRAINING CENTER FOR SPECIALISTS AND RESOURCES IN ORAL REHABILITATION, ID POSDRU/87/1.3/S/62208. Project co-financed from the European Social Fund through the Sectoral Operational Program Human Resources Development 2007-2013. Priority Axis 1 - Education and vocational training in support of the economic growth and development of the knowledge-based society. Major field of intervention 1.3.-Development of human resources in education and training, Decision 23904 // 29.10.2012

2.IMPLEMENTATION AND DEVELOPMENT OF MODERN

NEUROENDOVASCULAR THERAPY IN ROMANIAN MEDICAL PRACTICE, Lifelong learning program 2007-2013, Education and Culture, LEONARDO DA VINCI Lifelong learning program, Project no.: LLP-LdV/PLM/2007/RO/167, Contract no.: 11/2008

3. MEDVISE: PROFESSIONAL ADVICE IN MEDICAL SPECIALIZATIONS

4. CHRONEX-RD East-European Network of Excellence for Research and Development in Chronic Diseases

5. Graduate of Psycho-pedagogy course – Department for the training of teaching staff, "Alexandru Ioan Cuza" University of Iași, Diploma series D no. 0075829, 6.05.2004

6. Hospital management competence, School of Public Health and Health Management, Diploma series D no. SNSPMS: MS1/0876/18.10.2006.

In the same context of the academic activity, I contributed to the following textbooks for students:

1. SURGICAL ABILITIES. STUDY TEXTBOOK FOR THE I$^{st}$ YEAR. PROTOCOLS, ASSESSMENTS, authors: Mihaela Perţea, Camelia Tamaş, Dana Mihaela Turliuc (author), Publisher: PIM Iasi, 2017, ISBN 978-606-13-3589-3, 145 pages.
2. SURGICAL SKILLS. HANDBOOK MODULE I, PROTOCOLS, ASSESSMENTS, authors: Mihaela Perţea, Camelia Tamaş, Dana Mihaela Turliuc (author), Publisher: PIM Iasi, 2018, ISBN 978-606-13-4377-5, 123 pages.
3. ABILETÉS CHIRURGICALES. MANUEL D'ÉTUDE MODULE I. PROTOCOLES, ÉVALUATION, authors: Mihaela Perţea, Camelia Tamaş, Dana Mihaela Turliuc (author), Publisher: PIM Iasi, 2018, ISBN 978-606-13-4378-2, 109 pages.

Currently, I am a team member for two educational projects aimed to introduce new learning techniques for students (CLEVER - case-based learning and virtual cases to foster critical thinking skills of students), but also optimize the syllabus (BCIME - Building Curriculum Infrastructure in Medical Education) of the discipline programs from the Faculty of Medicine of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi.

**List of abbreviations**

| | |
|---|---|
| AC | arachnoid cyst |
| ACs | arachnoid cysts |
| AM | atypical meningioma |
| AMs | atypical meningiomas |
| BCC | basal cell carcinoma |
| BCCs | basal cell carcinomas |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| ENT | ear, nose and throat (surgery) |
| FD | fibrous dysplasia |
| GCS | Glasgow Coma Scale |
| GOS | Glasgow Outcome Scale |
| HE | haematoxylin and eosin |
| ICP | intracranial pressure |
| IH | intracranial hypertension |
| LI | labeling index |
| mRDS | modified Rankin Disability Score |
| MPHs | microporous polysaccharide hemispheres |
| MRI | magnetic resonance imaging |
| NC | nasopharyngeal carcinoma |
| NORs | nucleolar organizer regions |
| ON | optic nerve |
| ONs | optic nerves |
| OPI | orbitocranial penetrating injury |
| OPIs | orbitocranial penetrating injuries |
| PBE | peritumoral brain edema |
| PTSD | posttraumatic stress disorder |
| TBI | traumatic brain injury |
| TBIs | traumatic brain injuries |
| TN | trigeminal neuralgia |
| T1WI | T1-weighted image |
| WHO | World Health Organization |

# I.2.Neurosurgical research into intracranian tumors

## I.2.1. Neurosurgical research on intracranial meningiomas

### I.2.1.1. Correlations between histopathological characteristics of meningiomas and anatomical localization, demography and site of origin

***Background***

Meningiomas are tumors frequently encountered in the practice of the neurosurgeon, and in spite of the fact that they are in general benign and slow-growing tumors, they are sometimes aggresive from a histological point of view, which is why they are classified them into grade I, II or III according to the World Health Organization (WHO) classification (*Kolles et al., 2007*).

The term of *meningioma* was used for the first time by Harvey Williams Cushing (1869-1939) in 1922, in order to describe a tumor that was in close contact with the meninges, summing up all the variants of descriptives names thus far: *endothelioma, exothelioma, mesothelioma, meningo-exothelioma* or *arachnoid fibroblastoma* (*Bulsara et al., 2005, Singh et al., 2005*).

In 2016, the diagnostic criteria of meningiomas were reviewed, WHO introducing parenchymal cerebral invasion as an independent criterion for diagnosing of atypical meningiomas (AMs) (grade II meningiomas) (*Louis et al., 2016a, Louis et al., 2016b*). As a result, an important variability in the reported epidemiology of grade II meningiomas was noticed due to the variations in the interpretation of diagnostic criteria *(Bulleid et al., 2019*).

*Given the few studies currently available on the correlation between the histopathological characteristics and the anatomical site of the meningiomas in the intracranial space, we have conducted three original research which were published in international databases, and summary of the most important data are presented here, in the followings:*

Cucu AI, Costea CF, **Turliuc MD**, Ghiciuc CM, Costachescu B, Popescu R, Dumitrescu GF, Sava A, Tanase DM, Arbore-Sorete R, Poeata I. *Anatomical localization of intracranial grade II meningiomas in North-Eastern Romania. Our 25-years experience.* Romanian Neurosurgery 2019, 33(3):232-238.

Dumitrescu G, Indrei A, **Turliuc D**, Indrei L, Haba D, Alecu C, Păduraru D, Poeată I. *Corrélations démographiques et histopathologiques sur 103 méningiomes intracrâniens diagnostiques dans l'hopital clinique d'urgences "Prof. Dr. N. Oblu" Iasi.* Revista Română de Anatomie Funcțională și Clinică Macro-și Microscopică și de Antropologie 2009, 8(4):548-558.

Dumitrescu GF, Indrei A, Husseini M El, Haba D, Ianovici N, Poeată I, **Turliuc D.** *Posterior fossa meningiomas: correlation between site of origin and pathology.* Romanian Neurosurgery 2010, 17(3):327-338.

*This article has 1 ISI citation and a total of 5 citations.*

### I.2.1.1.1. Correlations between the intracranial localization of grade II meningiomas and histological subtypes

As regards the intracranial localization of grade II meningiomas and histological subtypes (atypical, clear cells and chordoid meningiomas), we have carried out a study in order to assess 143 patients from the Department of Neurosurgery of *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași, in the period 1990-2015. The data collected included: age, gender, anatomical localization and histological diagnosis (*Cucu et al., 2019b*) (Table 1).

**Table 1**. Characteristics of 143 patients with grade II meningioma (1990-2015) (from *Cucu et al., 2019b*)

| Characteristics | | Grade II n (%) |
|---|---|---|
| No. of patients | | 143 |
| Gender | female | 79 (55.2) |
| | male | 64 (44.8) |
| Age groups (years) | 20-29 | 3 (2.1) |
| | 30-39 | 9 (6.3) |
| | 40-49 | 23 (16.1) |
| | 50-59 | 42 (29.4) |
| | 60-69 | 41 (28.7) |
| | 70-79 | 22 (15.4) |
| | 80-89 | 3 (2.1) |
| Tumor localization | Convexity | 71 (49.7) |
| | Skull base | 44 (30.8) |
| | Parasagittal/falcine | 21 (14.7) |
| | Intraventricular | 7 (4.9) |
| Histological subtypes | Atypical meningioma | 135 (94.4) |
| | Clear cell meningioma | 6 (4.2) |
| | Chordoid meningioma | 2 (1.4) |

Out of 143 patients with grade II intracranial meningiomas, 55.2% (*n=79*) were female and 44.8% (*n=64*) were male. More than half of the patients were aged between 50-69, accounting for a percentage of 58.1% (*n=83*). When it comes to the distribution of the anatomical localization of intracranial meningiomas, most tumors were localized at convexity (49.7%), skull base (30.8%), parasagittal/falcine (14.7%) and intraventricular (4.9%). Furthermore, as regards the histological subtypes, most meningiomas were atypical (94.4%, *n=135*), followed by clear cell meningiomas (4.2%) and chordoid meningiomas (1.4%) (Table 1).

Our study demonstrated a predilection of the grade II meningiomas for the brain convexity (49.7%), in accordance with the previous studies (*Budohoski et al., 2018, Champeaux et al., 2017, Durand et al., 2009, Nanda et al., 2016, Zaher et al., 2013*) (Figure 1). This predilection of meningiomas for various anatomical localizations in the intracranial space was explained by some authors as the distinct embryological origins of skull and non-skull base dura mater (*Sade et al., 2007, Kepes, 1986*).

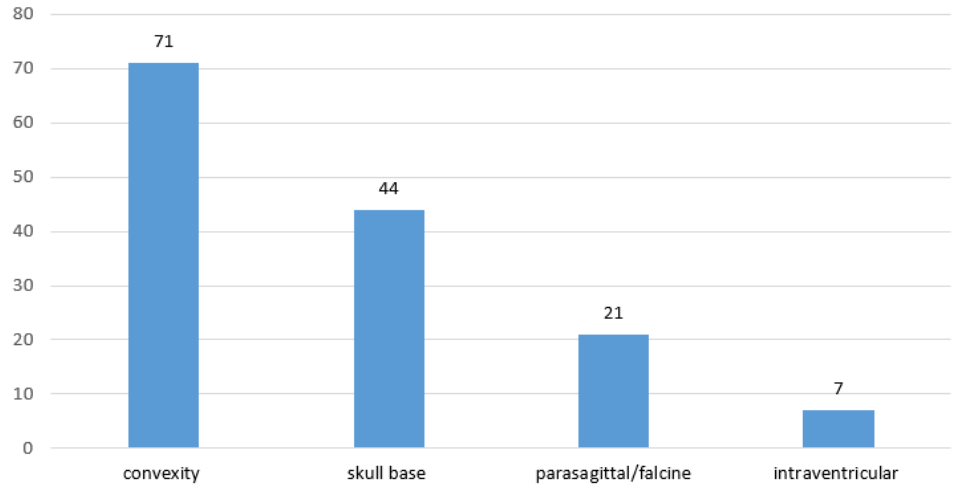


**Figure 1**. Incidence of grade II meningiomas according to anatomical localization (from *Cucu et al., 2019b*)

As regards the distribution of meningiomas in women and men, we have noticed a gender ratio of 1:1.2 (male:female) in the total number of patients, with a slight predominance in women, in accordance with other studies in the literature (*Barthélemy et al., 2018, Zaher et al., 2013*). If this ratio was maintained in meningiomas with parasagittal/falcine, skull base or intraventricular localizations, in case of convexity meningiomas we found a predominance in the female population than in the male one (43 vs. 28) (*Cucu et al., 2019b*) (Figure 2).

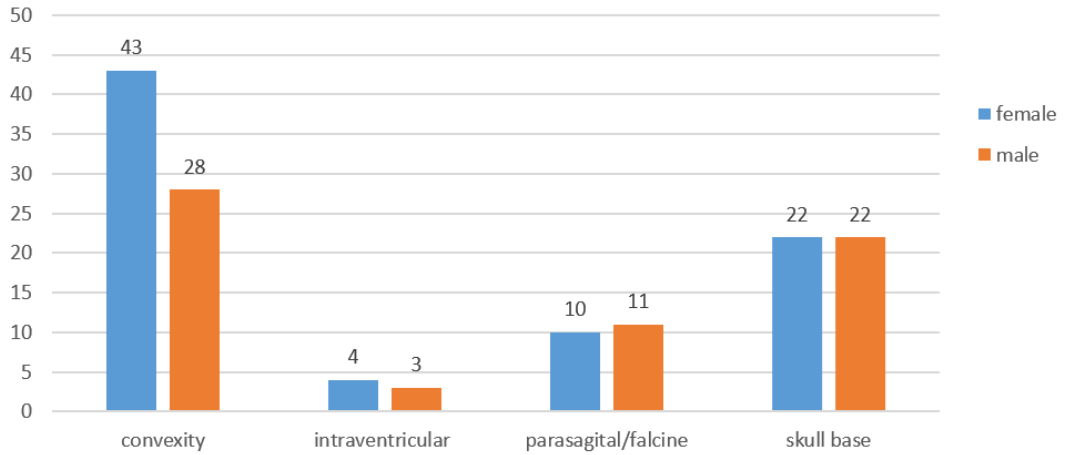


**Figure 2**. Incidence of grade II meningiomas according to gender (from *Cucu et al., 2019b*)

Out of all grade II meningiomas, AMs are the most common, representing a percentage of up to 30% of all meningiomas (*Pasquier et al., 2008, Pearson et al., 2008, Willis et al., 2005*). These can develop anywhere at the level of the skull, yet some authors have reported more frequent occurences in non-skull base locations, especially in cerebral convexity (*Hammouche et al., 2014, Mahmood et al., 1993, Modha and Gutin, 2005, Pasquier et al., 2008*), a fact which was also observed in our study (*Cucu et al., 2019b*).

When it comes to clear cell meningiomas, they are extremely rare tumors, the literature

reporting only 218 cases of such intracranial meningiomas thus far (*Li et al., 2016*). In our case, clear cell meningiomas represented a percentage of 4.2% of all grade II meningiomas. While the literature reports cerebellopontine angle as being the most common localization for clear cell meningiomas (*Tao et al., 2018, Wang et al., 2014*), in our study, these meningiomas were all localized at parasagittal and falcine regions (*n=6*) (*Cucu et al., 2019b*).

To conclude, our study highlighted a predominance of grade II meningiomas for cerebral convexity, followed by skull base, parasagittal, falcine (Figure 3) and intraventricular locations. Furthermore, we noticed a predilection for convexity meningiomas in the female population than in the male one. In order to establish the importance of pathological, genetic and embryologic factors in classifying the relationship between the anatomical localization of meningiomas and histological subtypes, further studies are necessary (*Cucu et al., 2019b*).

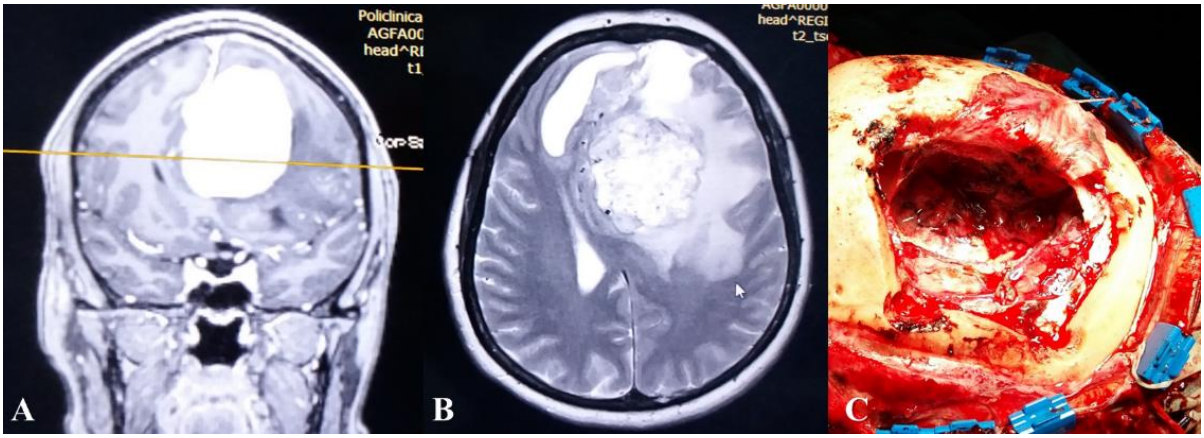


**Figure 3.** Preoperative coronal (A) and axial T1WI with contrast showing a left falcine meningioma (B). Postoperative images showing tumor bed after gross total resection (C). (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*) (from *Cucu et al., 2019b*)

### I.2.1.1.2. Correlations between demographic characteristics and histopathological features in intracranial meningiomas

Another study, in which we have evaluated the correlations between histopathological features and demographic characteristics, was conducted on 103 cases of intracranial meningiomas resected in the period from 1 January 2008 until 31 August 2009 in the Department of Neurosurgery within *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași (Table 2). Moreover, we have registered the patients' demographic data (age, gender), as well as the tumor type and histopathological grade (*Dumitrescu et al., 2009*).

**Table 2**. Distribution of intracranial meningiomas depending on their malignancy grade and histological subtypes (from *Dumitrescu et al.*, 2009).

| HISTOLOGICAL SUBTYPES | NO. OF CASES (%) |
|---|---|
| **GRADE I MENINGIOMAS** | 73 (70.87%) |
| - Meningothelial | - 35 (33.98%) |
| - Fibrous | - 20 (19.41%) |
| - Psammomatous | - 6 (5.82%) |
| - Transitional | - 3 (2.91%) |
| - Angiomatous | - 3 (2.91%) |
| - Secretory | - 2 (1.94%) |
| - With lipomatous metaplasia | - 2 (1.94%) |
| - Rich in lympho-plasmacytes | - 1 (0.97%) |
| **GRADE II MENINGIOMAS** | 27 (26.21%) |
| - Atypical | - 23 (22.23%) |
| - With clear cells | - 3 (2.91) |
| - Chordoid | - 1 (0.97%) |
| **GRADE III MENINGIOMAS** | 3 (2.91%) |
| **TOTAL** | **103 (100%)** |

Out of a total of 103 cases, 32.04% (*n=33*) were male and 67.94% (*n=70*) were female, with a male-female ratio of 2.12. When it comes to the correlation between tumor grade and average age at diagnosis, grade I meningiomas were associated with average ages of 56.28 years, grade II meningiomas with 58.19 years and grade III meningiomas with 69 years. The average age for patients was 55.4 years for women and 60.6 years for men, and the greatest incidence of meningiomas occured in the 50-59 age group. While grade I meningiomas were distributed approximatively equally between the two genders, in the case of grade II meningiomas, the highest occurence was in men (30.30%) than in women (24.28%). Furthermore, grade III meningiomas was recorded in the highest percentage in women, in the 60-69 age group (13.3%) (*Dumitrescu et al.*, 2009).

In our study, we also noticed that as the age at which the tumor is diagnosed grows, the possibility for the diagnosis of a tumor with a greater grade of malignancy also increases.

To conclude, our study demonstrated an incidence of the various histological types of benign meningiomas comparative with other studies, thereby demonstrating a predominance of meningothelial and fibrous subtypes. Moreover, depending on the patient's gender, there are differences in the distribution of histopathological subtypes of meningiomas, and these variations could have an etiological significance (*Dumitrescu et al., 2009*).

### I.2.1.1.3.Correlations between site of origin and pathology in the case of posterior fossa meningiomas

In another retrospective study carried out on 35 patients with posterior fossa meningiomas resected in the period 2005-2009 at the Department of Neurosurgery within *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași, we observed the correlations between site of origin and pathology in posterior fossa meningiomas (*Dumitrescu et al., 2010*).

We registered demographic data (age, gender), anatomical location of the meningioma at the

level of the posterior cranial fossa and histopathological diagnosis. Depending on the anatomical localization of the 35 tumors in our series, we classified anatomical localization thus: (1) *cerebellum convexity*, (2) *cerebellopontine angle*, (3) *petroclival*, (4) *foramen magnum* and (5) *unclassified meningiomas*.

Out of 35 patients, 29 had site of origin as follows: 14.28% on cerebellum convexity, 48.57% at the level of cerebellopontine angle, 11.42% petroclival, 8.57% were of foramen magnum, and 6 patients had gigantic meningiomas with large insertion at the level of the posterior fossa (17.14%) (Table 3).

**Table 3**. Posterior cranial fossa meningiomas: site of origin, gender and mean age of the patients (from *Dumitrescu et al., 2010*)

| Tumor location | Unclassified | | Cerebellar convexity | | Cerebellopontine angle | | Petroclival | | Foramen magnum | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pacient gender | F | M | F | M | F | M | F | M | F | M |
| Pacient mean age (years) | 52 | 43.33 | 64.25 | 49 | 50.93 | 49.33 | 55 | 50 | 52.66 | - |

Most meningiomas were of grade I (82.85%) with the most frequent histological subtypes fibrous (37.79%) and psammomatous (24.13%), followed by grade II meningiomas (11.42%) and grade III meningiomas (5.71%) (Table 4).

**Table 4**. Posterior cranial fossa meningiomas: site of origin, gender and histological degree of malignity (from *Dumitrescu et al., 2010*)

| Histological degree of malignity | Unclassified | | Cerebellar convexity | | Cerebello-pontine angle | | Petro-clival | | Foramen magnum | | No. cases (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | M | F | M | F | M | F | M | F | M | |
| Grade I | 1 | 2 | 4 | 1 | 13 | 3 | 3 | | 3 | - | 29 (82.85%) |
| Grade II | 1 | | | | 2 | | | 1 | | | 4 (11.42%) |
| Grade III | 1 | 1 | | | | | | | | | 2 (5.71%) |

Our study also confirmed other studies that demonstrated that posterior fossa meningiomas are more common in cerebellopontine angle, representing 24% of all the intracranial meningiomas (*Drevelegas et al., 2002*), and that foramen magnum and petroclival meningiomas are less common (*Louis et al., 2007*). In our series of patients, we noticed a predominance of grade I meningiomas, with a great variety of histological subtypes (Table 5).

**Table 5**. Posterior fossa meningiomas: sites of origin and histological subtypes (from *Dumitrescu et al., 2010*)

| Histological type | Un-classified | Cerebellar convexity | Cerebello-pontine angle | Petro-clival | Foramen magnum | No. cases (%) |
|---|---|---|---|---|---|---|
| Fibrous | 1 | 5 | 5 | | | 11 (37.79%) |
| Psammomatous | 2 | | 2 | 1 | 2 | 7 (24.13%) |
| Meningothelial | | | 3 | 1 | | 4 (13.79%) |
| Secretory | | | 2 | 1 | 1 | 4 (13.79%) |
| angiomatous | | | 3 | | | 3 (10.34%) |
| atypical | 1 | | 2 | 1 | | 4 (11.42%) |
| anaplastic | 2 | | | | | 2 (5.71%) |
| Total | 6 (17.14%) | 5 (14.28%) | 17 (48.57%) | 4 (11.42%) | 3 (8.57%) | 35 (100%) |

Chung *et al.* explain this histopathological variation of meningiomas by the fact that they occur from functional multipotent arachnoid cells (*Chung et al., 2007*), and Lee *et al.* consider that differentiated embryogenesis of the leptomeninges result in the predominance of a certain type of cell in the respective anatomical region (*Lee et al., 2006a*).

To conclude, our study demonstrated that posterior fossa meningiomas are different tumors, both demographically and histopathologically, from intracranial meningiomas localized in other areas. Moreover, we identified an association between the age and gender of the patients, as well as between the tumor histology and anatomical area of their cellular origin (*Dumitrescu et al., 2010*).

### I.2.1.1.4. Correlations between Ki-67 labeling index and demographic characteristics and tumor location in intracranial atypical meningiomas (WHO grade II meningiomas)

Cucu AI, Costea CF, **Turliuc MD**, Dumitrescu GF, Sava A, Poeata I. *Are there any correlations between demographic characteristics, tumor location and Ki-67 labeling index in intracranial atypical meningiomas (WHO grade II)?* Romanian Journal of Morphology and Embryology 2019, 60(2):567-572. (Impact Factor in 2018 = 1.5)

In a study retrospectively carried out on 29 patients with intracranial AMs operated in the Department of Neurosurgery within *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași, in the period from 2014 to 2016, we observed potential correlations between the patients' demographic characteristics, the anatomic location of the tumor and the Ki-67 labeling index (LI) (Table 6).

**Table 6.** Comparison of our results with other studies of Ki-67 LI in atypical meningiomas (from *Cucu et al., 2019c*)

| Authors | Year of publication | Country | No. of meningiomas | No. of AMs from all cases | Mean Ki-67 LI (%) in AMs |
|---|---|---|---|---|---|
| **Current study** | **2019** | **Romania** | **29** | **29** | **8.7** |
| *Al-Nuaimy et al.2012* | 2012 | Iraq | 50 | 5 | 5.4 |
| *Rao et al. 2009* | 2009 | India | 123 | 10 | 13.7 |
| *Uzüm and Ataoğlu, 2008* | 2008 | Turkey | 246 | 46 | 8.61 |
| *Karabagli and Sav, 2006* | 2006 | Turkey | 87 | 31 | 6.53 |
| *Roser et al., 2004* | 2004 | Germany | 600 | 45 | 9.95 |
| *Amatya et al., 2001* | 2001 | Japan | 146 | 27 | 8.1 |
| *Hsu et al., 1998* | 1998 | USA | 57 | 24 | 3.2 |

The majority of the intracranial meningiomas which were diagnosed in male patients expressed predominantly a value of Ki-67 LI ranging from 8% to 10% (Figure 4). Moreover, the mean Ki-67 LI demonstrated small variation in relation with gender (8.6% for female vs. 8.5% for male patients) (Figure 5) (*Cucu et al., 2019c*).

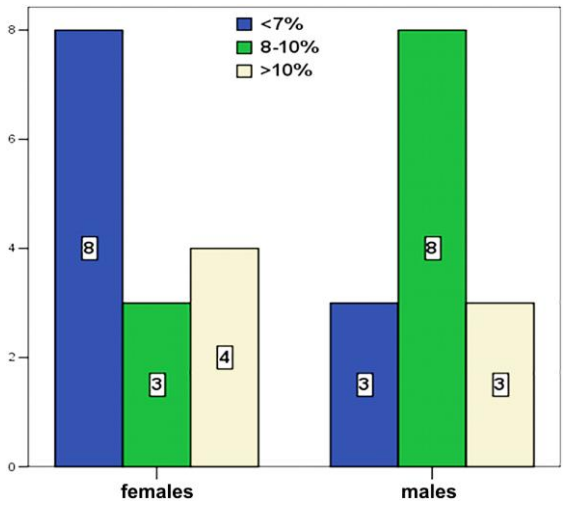


**Figure 4**. Ki-67 LI distribution according to patient gender (from *Cucu et al., 2019c*)

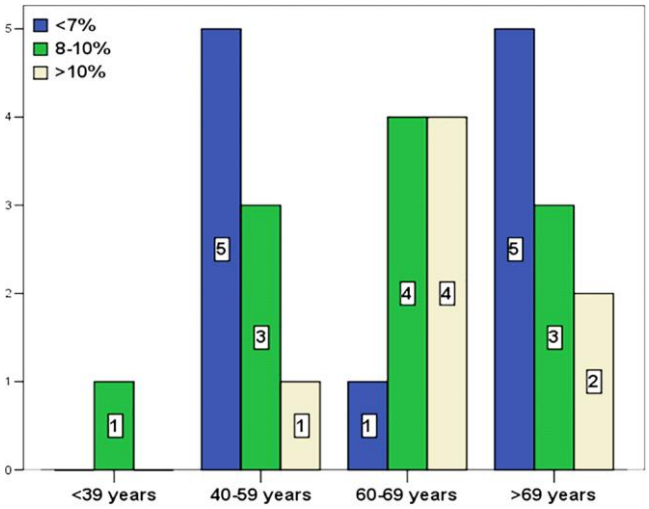


**Figure 5**. Ki-67 LI distribution according to patient age (from *Cucu et al., 2019c*)

When it comes to the anatomic location of intracranial AMs, 82.75% (*n=24*) of them were non-skull base, followed by 5 cases located at the skull base (Figure 6). Moreover, as regards the

relation between Ki-67 LI and tumor location, our study demonstrated that non-cranial base AMs had a higher mean Ki-67 LI in comparison with skull base AMs (8.9% vs. 8.2%) (Figure 7). Furthermore, in the case of non-skull base meningiomas, Ki-67 LI ranged from 6% to 15%, and in the case of skull base meningiomas from 7% to 10% (*Cucu et al., 2019c*).

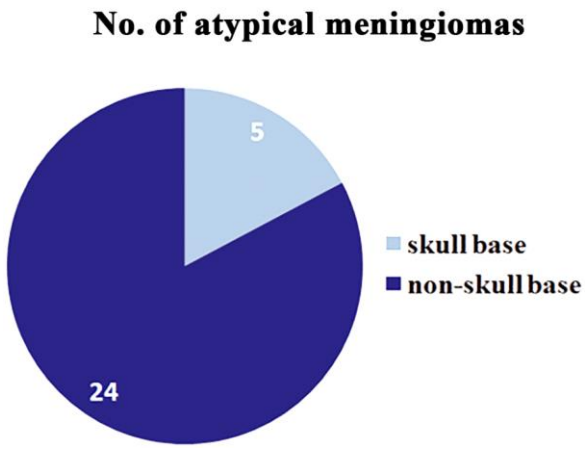


**Figure 6**. Anatomic location of intracranial atypical meningiomas (from *Cucu et al., 2019c*)

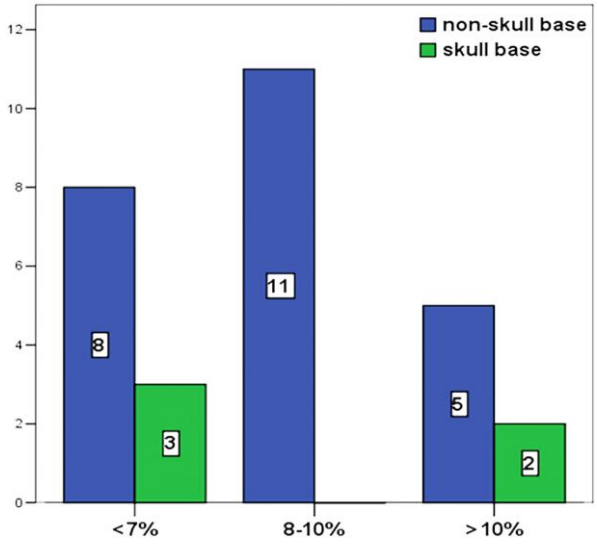


**Figure 7**. Ki-67 LI distribution according to the anatomic location of atypical meningiomas (from *Cucu et al., 2019c*)

In our study, we did not find any significant statistical relation between Ki-67 LI and patient's gender, as it was shown by other authors (*Hashemi et al., 2015, Nakasu et al., 1995, Pavelin et al., 2013, Salem et al., 2012*). Furthermore, we did not highlight any significant relation between Ki-67 LI and the patients' age, consistent with other studies (*Al-Nuaimy et al., 2012, Hashemi et al., 2015, Nakasu et al., 1995, Roser et al., 2004, Sandberg et al., 2001*).

When it comes to a possible correlation between Ki-67 LI and meningioma location, we did not find any significant relation, as reported by other studies (*Nakasu et al., 1995, Pavelin et al., 2013, Roser et al., 2004*). Nonetheless, we noted a higher prevalence of non-skull base meningiomas (Table 7, Figure 8), and this difference could be explained by the distinct embryological origin of skull base and non-skull base dura, which could lead to the predilection of more cases of different histological subtypes of meningioms (*Kepes, 1986, Lee et al., 2006a, Sade et al., 2007*).

**Table 7**. Ki-67 LI values according to patients' gender and tumor anatomic location (from *Cucu et al., 2019c*)

| | | Ki-67 LI <7% | Ki-67 LI 8–10% | Ki-67 LI >10% | Mean Ki-67 LI [%] | Ki-67 LI range [%] |
|---|---|---|---|---|---|---|
| Patients' gender | *Female* | 8 | 3 | 4 | 8.6 | 6–15 |
| | *Male* | 3 | 8 | 3 | 8.5 | 7–13 |
| Tumor anatomic location | *Non-skull base* | 8 | 11 | 5 | 8.9 | 6–15 |
| | *Skull base* | 3 | 0 | 2 | 8.2 | 7–10 |

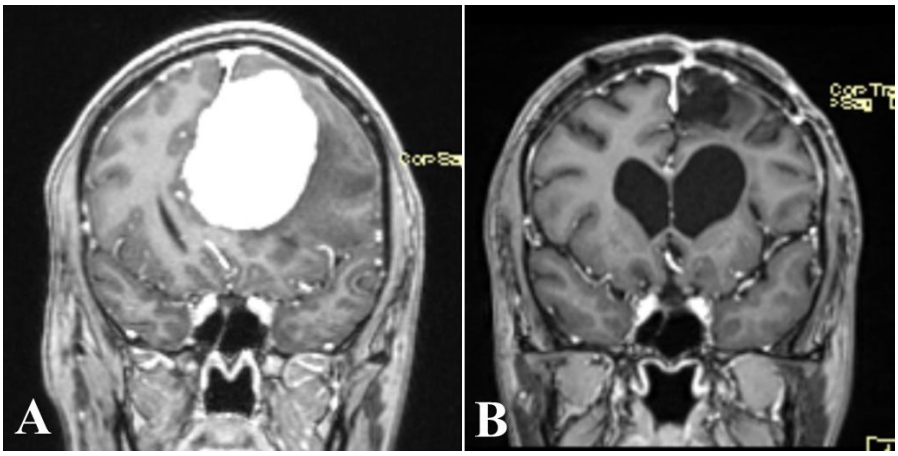


**Figure 8**. Preoperative coronal T1WI with contrast showing a left falcine atypical meningioma (A). Postoperative contrast-enhanced MRI images (B) (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

To conclude, the usage of Ki-67 LI in the arsenal of the pathological diagnosis of intracranial meningiomas is a supplement, not a substitute (Figure 9 and 10). Even though we have not demonstrated a statistically significant relation between Ki-67 LI expressed by AMs and the patients' age and gender or tumor anatomic location, intraumoral immunohistochemical expression of Ki-67 LI remain an important tool in routine histological evaluation and can be used to predict tumor behavior of meningiomas (*Cucu et al., 2019c*).

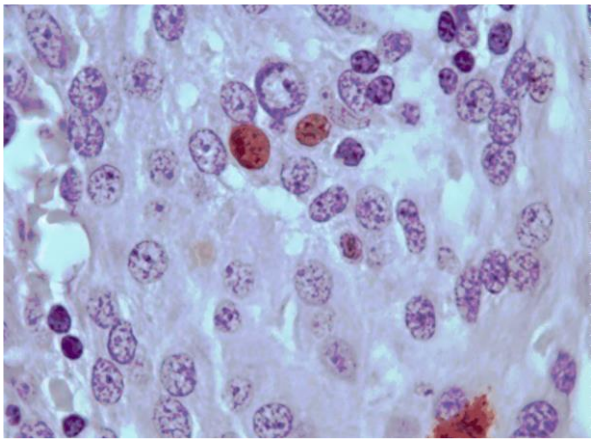

**Figure 9**. Female, 61 year-old, with a skull base AM: low expression of Ki-67 LI (6% nuclear staining) (immunohistochemical staining using MIB-1 clone, x100). *Courtesy of Dr. G. F. Dumitrescu,* (from *Cucu et al., 2019c*)

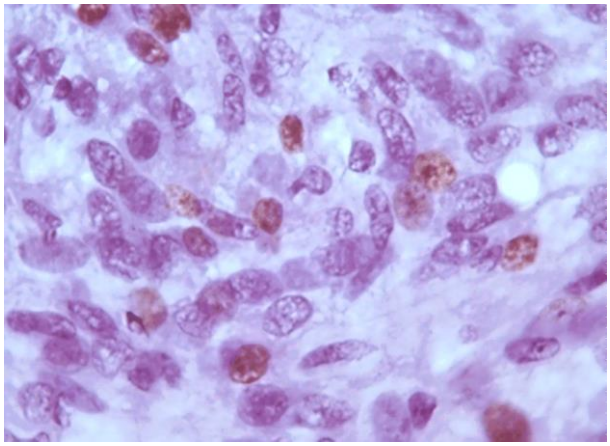

**Figure 10**. Male, 59 year-old, with a non-skull base AM: high expression of Ki-67 LI (13% nuclear staining) (immunohistochemical staining using MIB-1 clone, x100). *Courtesy of Dr. G. F. Dumitrescu,* (from *Cucu et al., 2019c*)

### I.2.1.2. Carcinogenic potential of ionizing radiation for the occurrence of intracranial meningiomas

***Background***

Even though over thirty years have passed since the Chernobyl nuclear disaster, studies have failed to fully elucidate the extent of the consequences. Moreover, the post-accident incidence of cerebral tumors, including meningiomas remains unclear to this day.

In the aftermath of the Chernobyl nuclear power plant explosion, the emissions emitted exceeded the contamination of the Nagasaki and Hiroshima nuclear bombs 100 times (*Nesterenko et al., 2009*), and the radioactive cloud covered the Northern Hemisphere, including the Romanian territory. In this regard, on our country's territory, the highest radioactive concentrations were recorded in the southern area and in the eastern part of the country (*Constantinescu and Bugoi, 1999*) (Figure 11), namely the geographical region which *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital of Iași serves, institution in which this study has been conducted (*Cucu et al., 2018*).

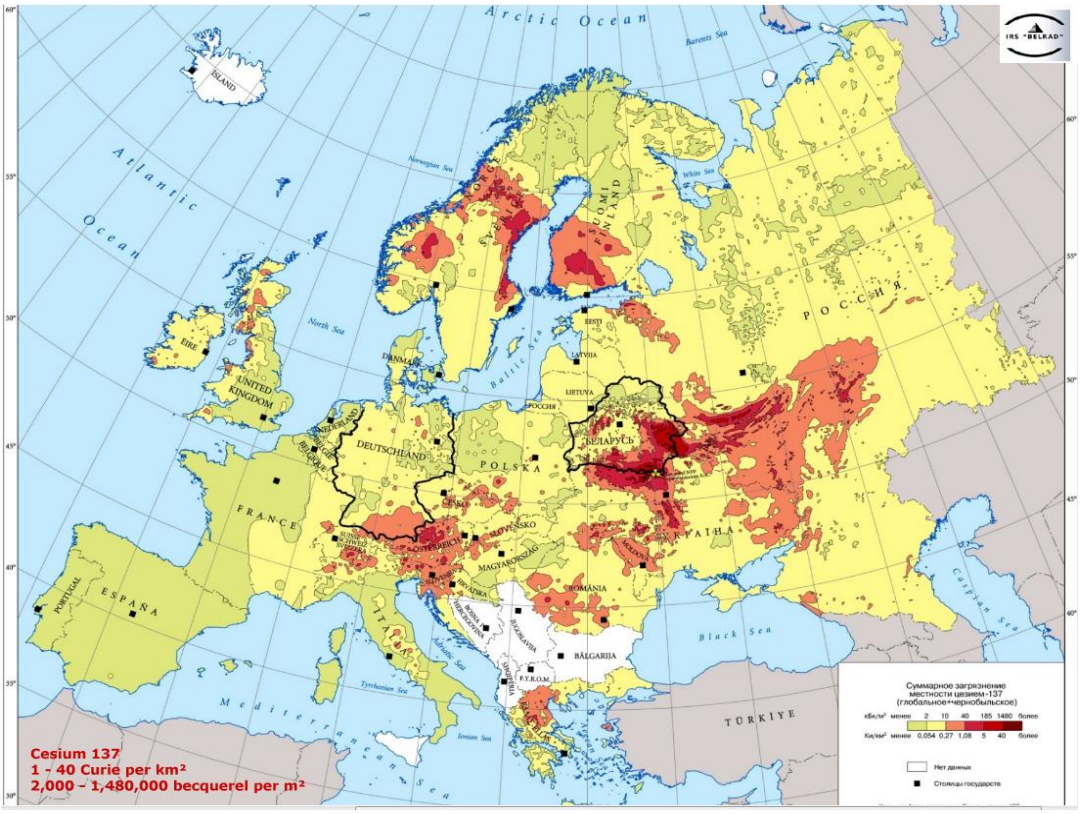


**Figure 11**. Areas in Europe most affected by Chernobyl radiation (1986). (public domain)

*As a result of our collaboration with colleagues from our department and with other colleagues from the Grigore T. Popa University of Medicine and Pharmacy, within the direction of the effect of the Chernobyl irradiation disaster on the occurrence of intracranial meningioma in north-eastern Romania, I have published one original research article in a journal indexed in ISI*

*Web of Science and summary of the most important data are presented here, in the followings:*

Cucu AI, Costea CF, Carauleanu A, Dumitrescu GF, Sava A, Scripcariu IS, Costan VV, Turliuc S, Poeata I, **Turliuc MD**. *Meningiomas related to the Chernobyl irradiation disaster in North-Eastern Romania between 1990 and 2015.* Rev Chim (Bucharest) 2018, 69(6):1562-1565. (Impact Factor in 2018 = 1.605)

*This article has 1 ISI citation.*

***Material and methods***

Our study has proposed to assess the meningioma behavior in the North Eastern area of our country (during 1990-2015), an area affected by the radioactive cloud. The study was observational, analytical and retrospective, conducted in our hospital and included 1287 patients with intracranial meningiomas resected in the period from 1990 to 2015 (*Cucu et al., 2018*).

***Results***

Out of the 1287 meningiomas, 832 cases (64.65%) were female and 455 (35.35%) were male. 30.30% of all cases, the 50-59 age group predominated (Figure 12), while of the total of 1287 meningiomas, 1027 cases (79.80%) were grade I meningiomas and 260 cases (20.20%) were grade II and III tumors.

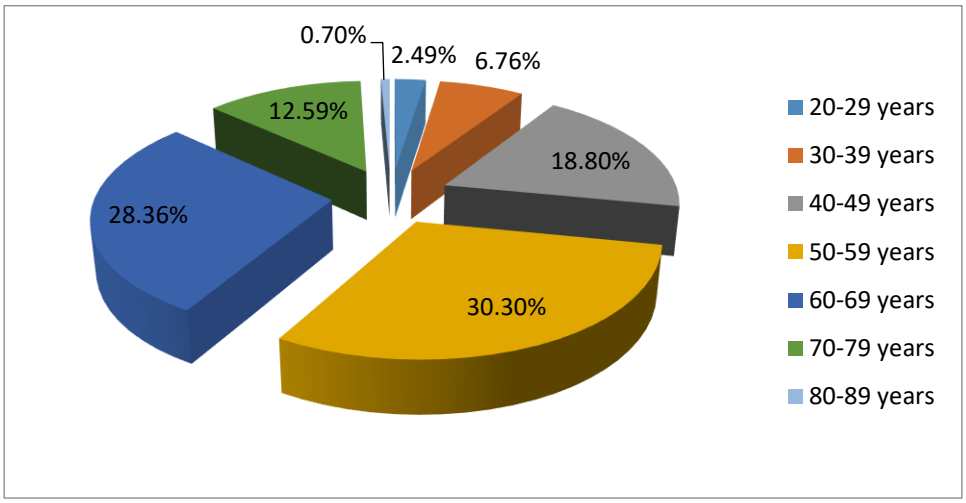


**Figure 12**. Distribution of meningiomas on age groups (1990-2015) (from *Cucu et al., 2018*)

While in each group more patients were recognized with grade I meningiomas than with grade II and III meningiomas, the exception was seen in the 80-89 years group, in which 44.44% of the tumors was grade I meningiomas and the rest with grade II and III (*Cucu et al., 2018*) (Figure 13).

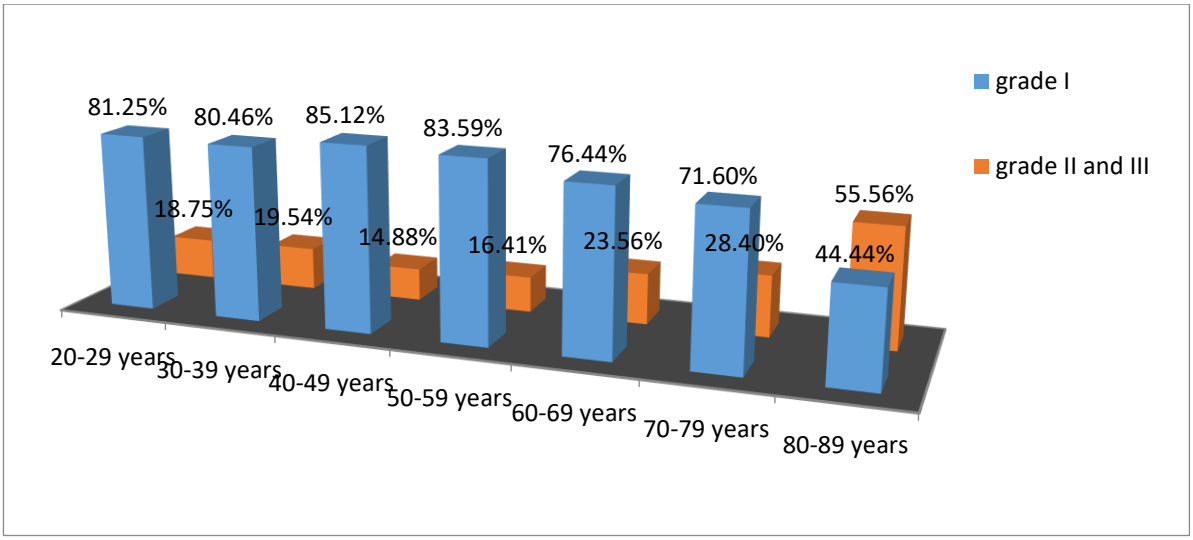


**Figure 13**. Distribution of cases by the degree of malignancy, according to age group (from *Cucu et al., 2018*)

In the period 1995-2006, 51.20% of all meningiomas were diagnosed, while in the following 9 years, the remaining cases, representing a percentage of 48.74%, were diagnosed, suggesting an increase in patients with intracranial meningioma after 2006 (*Cucu et al., 2018*).

***Discussions***

Over time, various authors have demonstrated the carcinogenic potential of ionizing radiation, both in studies conducted on animals (*Haymaker et al., 1972, Lonser et al., 2002, Traynor and Casey, 1971*), as well as on the survivors of the nuclear attacks from Nagasaki and Hiroshima who were exposed to an increased risk and developed intracranial meningiomas (*Sadamori et al., 1996, Shintani et al., 1999*). In terms of influence of the radiation resulting from the nuclear disaster on occurrence of cerebral cancer, the researches performed on the population affected showed a strong significant correlation. Thus, in the period 1987-2004, the incidence of CNS cancers in children up to the age of three has doubled, and in infants it increased 7.5 times (*Orlov et al., 2006, Orlov et al., 2001, Cucu et al., 2018*). Moreover, in the period 1987-1991, immediately after the accident, compared with the period 1981-1985 before Chernobyl, the rate of children with cerebral cancer increased with 63.7% (*Orlov, 1993, Orlov, 1995, Orlov and Sharevsky, 2003*).

As regards our study, we noticed an increase of meningiomas in the period 1993-1996 and 2007-2015, namely 7-10 years and 21-30 years, respectively, after the nuclear catastrophe (*Cucu et al., 2018*) (Figure 14). This period of time between the first exposure to radiation and the appearance of brain tumors has been called in the literature as *the latency period*, and regarding the occurrence of cerebral cancer, several authors found a latency time of ten years (**UNSCEAR, 2000*), while other studies founded that solid cancer occur only decades after the nuclear disaster (**UNICEF, 2002, Cucu et al., 2018*). Other authors detected a mean period of twenty years (*Hatch et al., 2005, *UNDP and UNICEF, 2002*).

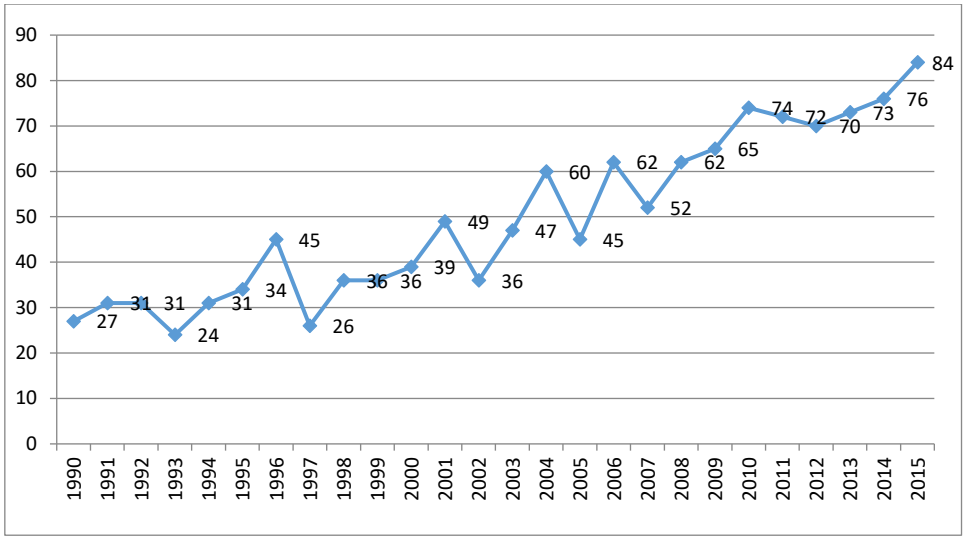


**Figure 14**. Annual incidence of the cases reported between 1990 and 2015 (from *Cucu et al., 2018*)

The time chart for grade I meningiomas highlights a variation in the total number of patients, without recording a trend of the cases registered annually (*Cucu et al., 2018*) (Figure 15).

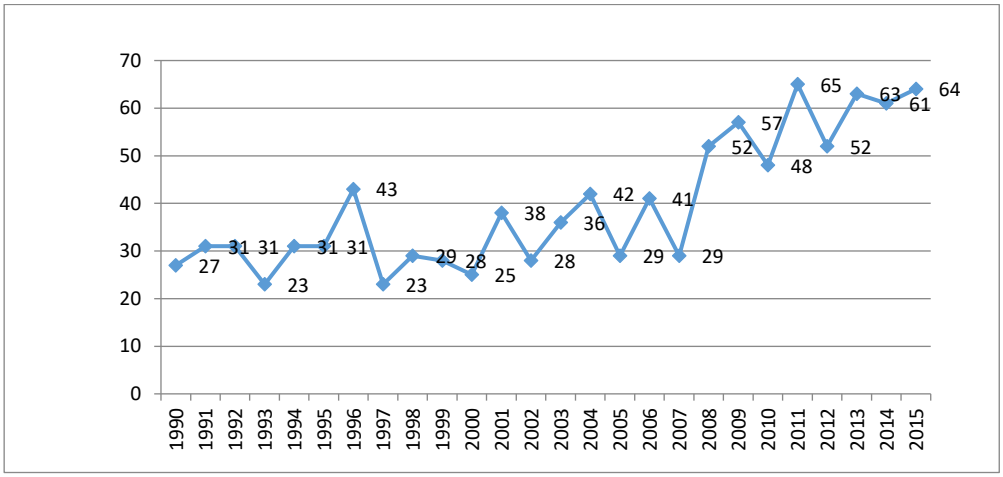


**Figure 15**. Annual incidence of grade I meningiomas (from *Cucu et al., 2018*)

For grade II and III meningiomas, the graph indicates their relative absence until 1995, with an upward trend in the period 1996-2000, which corresponds to a period of 10-14 years after disaster (Figure 16). This is followed by the variation in the number of cases after 2000, with irregular decreases and increases in the patients diagnosed (*Cucu et al., 2018*). (Figure 16). By correlating irradiation with histopathological grade of tumors, some authors demonstrated, on 80.160 atomic bomb survivors from Nagasaki and Hiroshima, a predominance of benign meningiomas (*Preston et al., 2002*), while other authors confirmed that radiation-induced meningiomas are most commonly AMs and anaplastic meningiomas (*Shoshan et. al, 2000, Soffer et al., 1983, Rubinstein et al., 1984*).

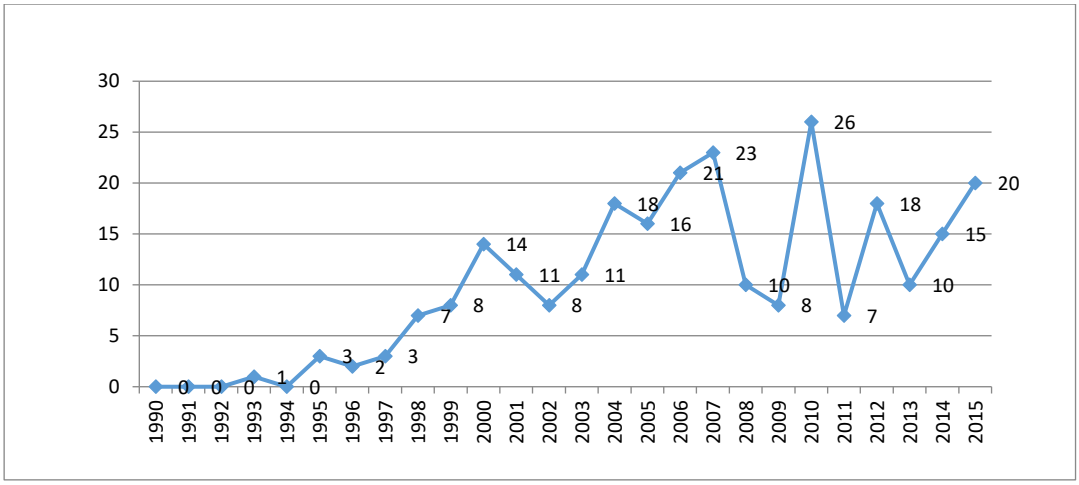


**Figure 16**. Annual incidence of grade II and III meningiomas (from *Cucu et al., 2018*)

***Conclusions***

In the period 1990-2015 we noticed an increase of meningiomas, with 2 peaks: one in the period 1993-1996 and the second in the period 2007-2015, which corresponds to a period 7-10 and 21-30 years, respectively, after the nuclear disaster. If, for grade I meningiomas, there is no cyclization or tendency, for grades II and III we can say that there was an upward trend in the 1996-2000 interval, which corresponds to a period of 10-14 years after Chernobyl. Through these results, our study has shown that, in the population of North-Eastern Romania, the number of intracranial meningiomas is constantly increasing, also being influenced by the ionizing radiations from Chernobyl. Furthermore, the fact that the incidence of intracranial meningiomas began to increase 20 years after the accident could suggest that this period of time could represent the latency period for the occurrence of radiation-induced intracranial meningiomas (*Cucu et al., 2018*).

### I.2.1.3. Studies on prognostic factors in atypical intracranial meningiomas

***Background***

Meningiomas represent one third of all primary CNS tumors (*Louis et al., 2000*). If, conformable to the 2007 WHO classification, AMs represented 5-7% of all meningiomas (*Louis et al., 2007*), currently, they represent approximately 20% of all meningiomas (*Bagshaw et al., 2017*, *Pasquier et al.2008, Pearson et al., 2008, Perry et al., 2007*).

AMs represent an intermediate subtye between grade I and grade III meningiomas, being known for tumor recurrence after surgery (*Modha and Gutin, 2005*) as well as for their increased mortality and morbidity (*Mangubat and Byrne, 2010*).

The relatively low incidence of these tumors, as well as the inconsistent histopathologic criteria over time, has led to a difficult comprehension of the treatment of these tumors, especially of the prognostic factors when it comes to relapse (*Hammouche et al., 2014*). Thus, various authors have attempted to find the prognostic factors in AMs, dividing them into: (1) *demographic factors* (gender, age), (2) *clinical factors*, (3) *factors related to the tumor location*, tumor dimensions and histological features, (4) *factors related to radiological features* and (5) *factors related to extent of resection*. Also,

in recent years, an increase in atypical meningioma (AM) diagnoses was observed (*Dolecek et al., 2012, Pearson et al., 2008).* From this point of view, an area of interest for me has been the prognostic factors in intracranial AMs.

*In the direction of research on atypical meningiomas, I have published 1 original research article in a journal indexed in ISI Web of Science and 5 articles (3 original papers and 2 reviews) in journals indexed in other international databaseses. There articles are part of approaching the prognostic factors that influence relapse and survival rate of patients diagnosed with intracranial atypical meningiomas and a summary of the most important data is presented here, in the followings:*

Cucu AI, **Turliuc MD**, Carauleanu A, Poeata I, Costea CF, Dumitrescu GF, Sava A. *Chemical aspects of peritumoral cerebral edema in atypical meningiomas.* Rev Chim (Bucharest) 2018, 69:2804-2807. (Impact Factor in 2018 = 1.605)

Cucu AI, Costea CF, Poeata I, Costachescu B, Dumitrescu GF, Sava A, **Turliuc MD**. *Anatomical localization of atypical meningiomas: our experience on 81 patients*. Revista Medico-chirurgicală a Societății de Medici și Naturaliști din Iași 2018, 122:744-752.

Cucu AI, Costea CF, **Turliuc MD**, Dumitrescu GF, Sava A, Poeata I. *Mirror, mirror on the wall, who's the fairest of them all? Atypical meningioma associated with multiple meningiomas*. Romanian Neurosurgery 2018, 32(4):563-572.

Cucu AI, **Turliuc MD**, Costea CF, Dumitrescu GF, Sava A, Poeata I. *Atypical meningiomas of cerebellopontine angle. A five case series*. Revista Medico-chirurgicală a Societății de Medici și Naturaliști din Iași 2018, 122(3):533-545.

Cucu AI, Costea CF, Poeată I, **Turliuc DM**. *Prognostic factors in atypical meningioma*. Romanian Neurosurgery 2017, 32(2): 165-171.

Cucu AI, **Turliuc DM**, Costea CF, Costachescu B, Malaimare AE, Blaj LA, Trandafir V, Danca C, Poeata I. *Pathways of metastatic spread in meningiomas.* Romanian Neurosurgery 2019, 33(1):12-16.

***Results and discussions***

In a study carried out in the period 2000-2017 (*Cucu et al., 2018a*) we have retrospectively analyzed 25 patients with AMs of convexity, operated and histologically confirmed in *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital from Iași. We determined which of the demographic, clinical, anatomopathological and neuroimaging factors correlate with peritumoral brain edema (PBE) encountered in AMs. The patients underwent a head-MRI prior to surgery and we have subsequently correlated potential links between PBE and demography (age and gender), symptomatology, localization, meningioma volume, brain invasion, shape of the meningioma margins, as well as MRI features (signal intensity on T2WI, aspect of the contrast and heterogeneity of the tumor) (*Cucu et al., 2018a*).

On the MRI scan images we calculated the approximate meningioma volume, utilizing the "spheroid formula: *volume = 4/3 π abc*, with the help of the maximal perpendicular diameters of the meningioma from the axial MRI section (radii a and b) and diameter of the meningioma from the coronal MRI section (radius c)" (*Cucu et al., 2018a*) (Figure 17).

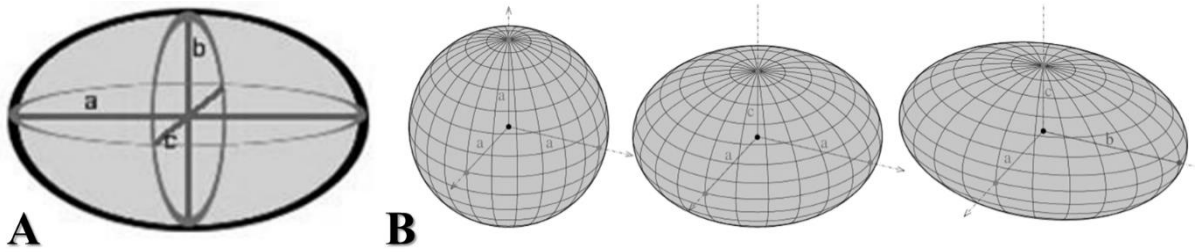


**Figure 17**. Calculation of the volume of an ellipsoid (A). Examples of ellipsoids (B). (public domain)

PBE was assessed as a high signal adjacent to the meningioma on T2WI and classified by Hale scale (*Hale et al., 2018*) (Figure 18).

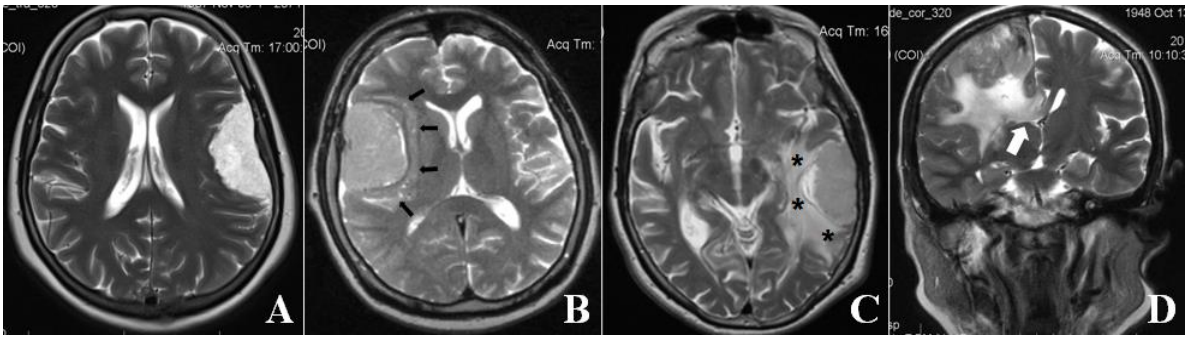


**Figure 18**. "Edema scale (Hale scale): 0 - *no edema* (A), 1- *mild edema*, with crescent or rim of increased T2WI images surrounding the tumor (black arrows) (B), 2 - *moderate edema* with more extensive increased T2WI images (black asterisk) (C), 3 - *severe edema* with mass effect and compression the lateral ventricle (white arrow) (D)" (*Hale et al., 2018*) (from *Cucu et al., 2018a*)

In our study, out of the 25 cases of meningiomas, 60% were with brain edema, with a gender ratio of 1: 1.1 (female:male), in accord with other authors reporting the PBE as being frequently encountered in AMs (*Kim et al., 2011, Mattei et al., 2005*). Out of the 15 cases of meningiomas with PBE, most patients suffered from a severe form (*n=8*), followed by moderate edema (*n=3*) and mild edema (*n=4*) (*Cucu et al., 2018a*).

A significant relation was found between age and contrast enhancement, in the sense that, in the case of patients older than 60, tumors intensely enhance the contrast substance. As regards tumor volume and relation with edema, we found no statistical significance, in accordance with other authors who reported the same conclusion (*Inamura et al., 1992, Gurkanlar et al., 2005, Vries and Wakhloo, 1993*).

We also assessed the meningioma margins, considering them *irregular* (with nodularity and anfractual margins) and *smooth* (no nodularity or irregularities and smooth edges). Out of a total of 25 AMs, 56% (*n=14*) had irregular edges (Table 8). Moreover, we found a statistical significance

between PBE and irregular margins, in agreement with other studies (*Kim et al., 2011, Simis et al., 2008*).

**Table 8**. Relation between meningioma margins and peritumoral brain edema (from *Cucu et al., 2018a*)

| ***Tumor margin*** | ***Edema*** | ***No edema*** | ***Total*** |
|---|---|---|---|
| **Smooth** | 4 (36.36%) | 7 (63.63%) | 11 (100%) |
| **Irregular** | 11 (78.57) | 3 (21.42) | 14 (100%) |
| **Total** | 15 (60%) | 10 (40%) | 25 (100%) |

In this regard, some studies considered that one of the most important factors in the occurrence of PBE is the interface between tumor and cerebral parenchyma (*Ildan et al., 1999, Simis et al., 2008*). Furthermore, Simis *et al.* considered that an irregular interface between brain and tumor favors the occurence of PBE and brain invasion (*Simis et al., 2008*).

To conclude, we could consider irregular meningioma margins to be an important predictor factor for brain edema, which can influence the clinical course of patients (*Cucu et al., 2018a*).

In another study published in 2018 (*Cucu et al., 2018b*), we analysed 81 patients admitted to *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași in the period 2010-2016, with histopathological diagnosis of AM. The data monitored included: demographic data (age, gender), anatomical localization, dural venous sinus invasion and tumor laterality (right-left) (Table 9).

Out of a total of 81 patients with intracranial AMs, 55.5% (*n=45*) were female and 44.5% (*n=36*) were male, with a male to female ratio of 1: 1.3. The mean age of surgery was 62.1 years.

**Table 9**. Summary of patient characteristics (from *Cucu et al., 2018b*)

| Characteristic | |
|---|---|
| No. of patients | 81 |
| **Age (years)** | |
| Mean | 62.1 |
| Median | 64 |
| Range | 20-85 |
| **Age groups** | |
| <39 | 3 (3.7%) |
| 40-59 | 28 (34.5%) |
| 60-69 | 23 (28.3%) |
| >69 | 27 (33.3%) |
| **Sex** | |
| Female | 45 (55.5%) |
| Male | 36 (44.5%) |
| **Tumor location** | |
| Convexity | 34 (41.9%) |
| Parasagittal/falcine | 26 (32%) |
| Skull base | 13 (16%) |
| Posterior fossa | 7 (8.6%) |
| Intraventricular | 1 (1.2%) |
| **Laterality** | |
| Right | 32 (39.5%) |
| Left | 28 (34.5%) |
| Midline | 10 (12.3%) |
| Midline-right | 4 (4.9%) |
| Midline-left | 7 (8.6%) |
| **Venous sinus involvement** | |
| yes | 18 (22.2%) |
| no | 63 (77.7%) |

Furthermore, we identified 75.3% (*n=61*) non-skull base meningiomas and 24.6% (*n=20*) skull base meningiomas. From the point of view of anatomical localization, 41.9% (*n=34*) were on convexity, 32% (*n=26*) parasagittal/falcine, 16% (*n=13*) on skull base (anterior and middle cranial fossa), 8.6% (*n=7*) posterior cranial fossa and 1.2% (*n=1*) intraventricular meningiomas. In 22.2% of the cases (*n=18*) dural venous sinus invasion was present (*Cucu et al., 2018b*) (Table 10).

**Table 10**. Incidence of atypical meningiomas by site of origin (from *Cucu et al., 2018b*)

| **Midline** | | **Lateral** | | | |
|---|---|---|---|---|---|
| Tuberculum sellae | 1.2% (1) | Orbital roof | 1.2% (1) | Convexity | 41.9% (34) |
| Cavernous sinus | 4.9 (4) | Orbito-sphenoidal | 1.2% (1) | Parasagittal/ falcine | 32.0% (26) |
| Petro clival | 1.2% (1) | Lateral / middle sphenoid wing | 6.1% (5) | Intraventricular | 1.2% (1) |
| | | Lateral tentorial | 8.6% (7) | | |

In our study, we found a predominance of AMs for non-skull base location (75.3%), compared to skull base meningiomas which represented 24.6% of the total of AMs studied. According to our classification (Table 10), within non-skull base meningiomas, the most common were at the level of brain convexity (41.9%) (Figure 19), followed by parasagittal/falcine location (32%), in agreement with the studies in the literature (*Budohoski et al., 2018, Champeaux et al., 2017, Nanda et al., 2016, Zaher et al., 2013*).

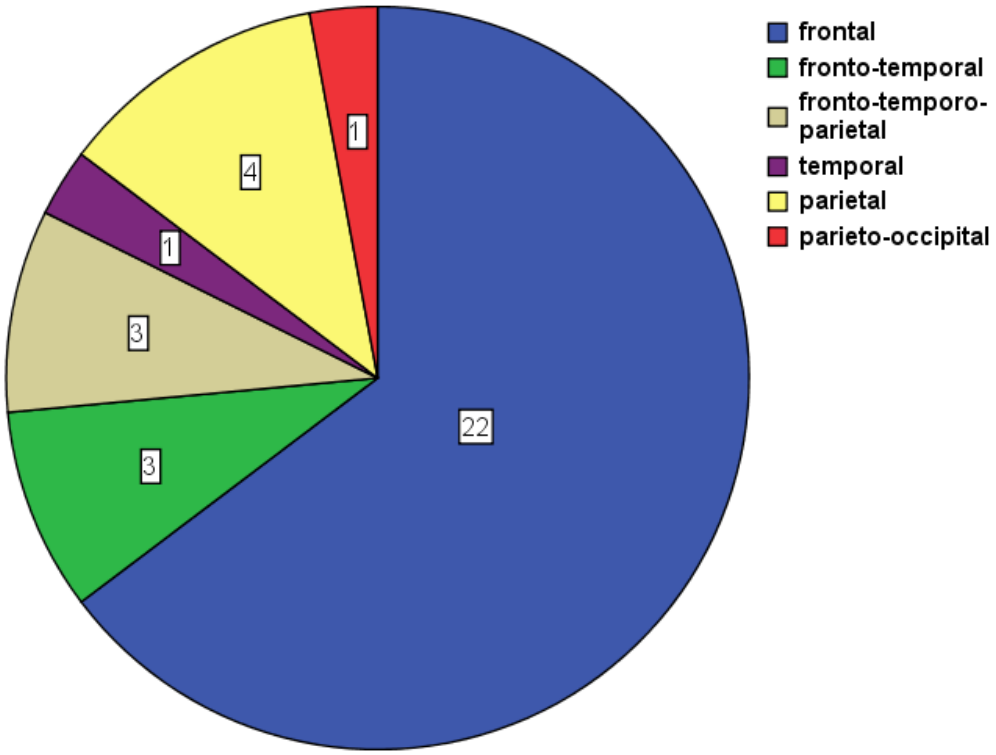


**Figure 19**. Incidence of atypical meningiomas of convexity according to anatomical location (from *Cucu et al., 2018b*)

When it comes to the relevance of the anatomic localization of AMs, embryological studies

have shown that the meninges covering the brainstem have a different origin than the meninges at the level of convexities and lateral skull base, thus explaining the aggressive behavior of certain meningiomas compared with others in different anatomical locations, given the fact that this differential meningeal embryogenesis could lead to predominance of one arachnoid cell type over other location (*Sade et al., 2007*).

In one of his studies, McGovern *et al.* concluded that intracranial benign meningiomas arising outside the cranial base are more prone to relapse at a higher grade than cranial base meningiomas. Also, he considers that benign non-cranial base meningiomas have a higher rate of cell proliferation than benign meningiomas arising from cranial base (*McGovern et al., 2010*). The authors suggest genetic differences as the basis of the differences between the different behaviors of cranial base and non-cranial base meningiomas.

To conclude, our study has shown a predominance of AMs in the brain convexity (Figure 20), in agreement with other studies in the literature. Furthermore, we believe that additional studies of immunohistochemistry and genetics are necessary in order to elucidate the importance of genetic factors in AMs predilection for non-skull base anatomic locations, and this could lead to the development of specific therapies for patients suffering from aggressive meningiomas (*Cucu et al., 2018b*).

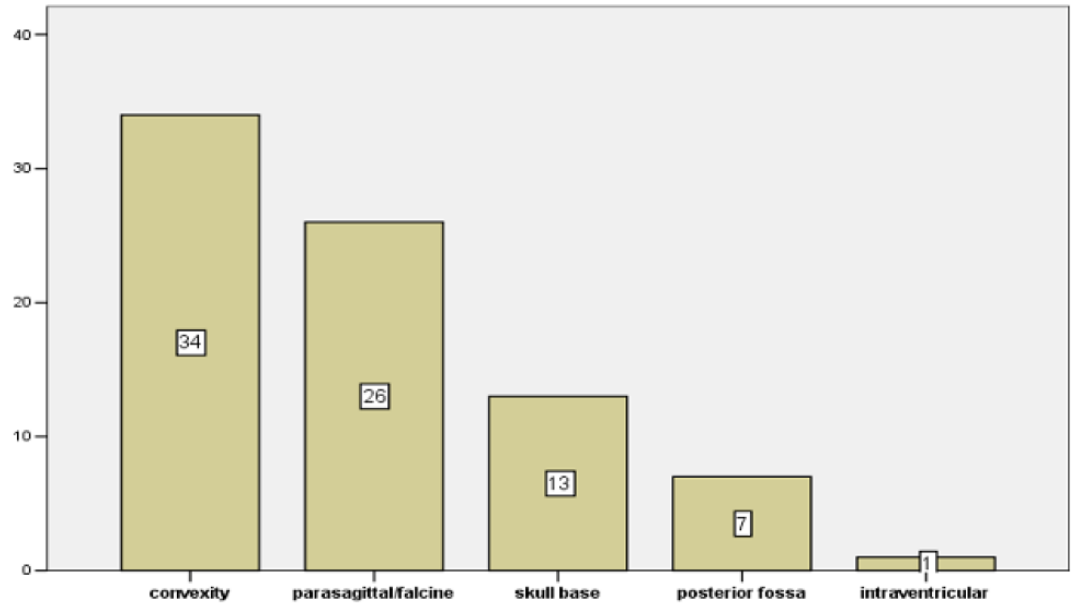


**Figure 20**. Incidence of atypical meningiomas according to anatomical location (from *Cucu et al., 2018b*)

In one of our previous studies (*Cucu et al., 2018c*) we monitored, for 3 years (2010-2013), 3 patients with multiple meningiomas who underwent surgey in the *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital of Iași. The patients were adults, with diagnosis of ≥ 2 separate meningiomas on head-MRI scan, one of which was resected and had the anatomopathological diagnosis of AM (Table 11).

**Table 11**. Clinical data of patients with multiple meningiomas, of which one was an atypical meningioma ( from *Cucu et al., 2018c*)

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Location (AM) | diaphragm sellae meningioma | left transverse sinus meningioma | parieto-occipital meningioma |
| Location of the other meningiomas | right parietal left parietal | left parasagittal | superior sagittal sinus meningiomatosis |
| Age, sex | M, 64 years | F, 65 years | F, 73 years |
| Symptoms | visual acuity decreased visual acuity in both eyes | intracranial hypertension syndrome, cerebellar syndrome | spastic paraparesis, intracranial hypertension syndrome |
| Ki - 67 | 4% | 4.7%, with 7.59% on a field | 6% |

As regards the distribution of multiple meningiomas in the intracranial space, according to the studies, the great majority of patients have a major meningioma which is accompanied by one or several smaller meningiomas (*Domenicucci et al., 1989, Huang et al., 2005*). This was also encountered in the patients who were subjected to our study. From this point of view, Huang *et al.* considered that several different-sized tumors in the same pacient with multiple meningiomas represented an indication of the fact that meningiomas can develop at different times and that there is a possibility for an initial major meningioma to disseminate and form multiple foci in the subarachnoid or subdural space (*Huang et al., 2005*).

Furthermore, when it comes to the histopathology of multiple meningiomas, the great majority of these tumors are benign (grade I) and have a uniform histology, atypical and anaplastic meningiomas (grade II and grade III) being rare (*Koh et al., 2001*). Some studies have shown that the same patient can develop meningiomas of different grades as well as of different histological characteristics (*Huang et al., 2005, Mocker et al., 2011*).

In 2018, Tsermoulas *et al.* reported that approximatively 1 in 5 patients with more than 2 resected intracranial meningiomas had meningiomas of different grades, with different histological subtypes (*Tsermoulas et al., 2018*). Thus, from this point of view, some authors believe that these findings demonstrate that different origins of meningiomas from multiple foci and that their multiplicity does not in fact represent tumor cells migration through the subarachnoid space (*Mocker et al., 2011, Neuss et al., 1988*).

Moreover, as regards the existence of an AM within multiple meningiomas, Mocker *et al.* believes this to be extremely rare (*Mocker et al., 2011*), the literature reporting only a few cases of benign histological meningiomas mixed with AMs (*Butti et al., 1989, Mocker et al., 2011, Oshita et al., 2007, Tomita et al., 2003*).

In terms of recurrence, in our series, only one patient developed tumor recurrence after 2 years and none of the other unoperated meningiomas did not grow in size during 3 years follow-up. Our results are in agreement with Wong *et al.* who did not notice tumor growth rate in pacients with multiple meningiomas to be higher than the growth rate of incidentally found solitary meningiomas

(*Wong et al., 2013*).

To conclude, even though no treatment strategy in multiple meningiomas has been established, our recommendation is to treat symptomatic meningiomas and to apply the conservative approach, more precisely neuroimaging follow-up for the asymptomatic tumors (*Cucu et al., 2018c*).

### I.2.1.4. Hyperostosis in intracranial meningiomas: ancient examinations from the perspective of modern neurosurgery

***Background***

Meningiomas are intracranial tumors which have been known for a long time, probably also due to the hyperostotic modifications that could sometimes lead to grotesque cranial deformities. Even though these types of tumors most commonly originate from arachnoid cells which are attached to the dura mater (*Di Cristofori et al., 2018*), in 25-50% of the cases the meningiomas will produce changes on the surrounding bone (*Pieper et al., 1999, Talacchi et al., 2011*).

If, in some cases, the tumors erode or infiltrate the adiacent bone, in other cases they could lead to hyperostotic changes (*Di Cristofori et al., 2018*) (Figure 21). The first to describe this interaction between meningiomas and bone was Harvey Cushing, in 1922 (*Cushing, 1922*). Even though these hyperostotic changes have been researched since the beginning of the 19th century, clinical significance of hyperostosis encountered in meningiomas is still controversial nowadays (*Bikmaz et al., 2007, Min et al., 2005, Pieper et al., 1999, Ringel et al., 2007, Shrivastava et al., 2005*).

In one of our reviews, published in 2019, we studied the hyperostotic changes within intracranial meningiomas, from the Steinheim cranium and "pharaonic meningiomas" from Egypt, to Harvey Cushing's first plausible explications regarding the mechanism of hyperostosis (*Cucu et al., 2019a*).

*The results of this review have been published in a journal indexed in ISI Web of Science and the summary of the most important data is presented here, in the followings:*

Cucu AI, Costea CF, Perciaccante A, Carauleanu A, Turliuc S, Costachescu B, Poeata I, **Turliuc MD.** *The history of Arachne through historic descriptions of meningiomas with hyperostosis: from prehistory to the present*. World Neurosurgery 2019, 128:37-46. (Impact Factor in 2018 = 1.723)

From an archeological perspective, intracranial meningiomas could be said to have been primarly identified as changes of the ectocranial table which, in fact, represented *paleopathological hallmarks* of these lesions (*Brothwell and Brothwell, 2016*). Thus, intracranial meningiomas with hyperostosis originating in the Paleolithic have been recorded worldwide.

*Homo steinheimensis or Steinheim skull*

Of all the crania with hyperostotic modifications produced by intracranial meningiomas, the oldest has been identified in the *Steinheiman der Murr*, in 1933 (Figure 21). It was later re-examined by Czarnetzki *et al.* from Eberhard-Karls University of Tübingen, who proved in 2003, that the owner

of the cranium had a meningioma (*Czarnetzki and Schwaderer, 2003*).

The authors of the study dated it to 365.000 BC, the skull with its bone changes being considered the earliest registration of a *Homo erectus* meningioma (*Okonkwo and Laws, 2009, Wolpoff, 1999, Ziegler, 1999*). The group of researchers found that Pleistocene human would have a meningioma with a mediolateral dimension of 43 mm, an anteroposterior dimension of 51 mm, and a depth of 25 mm. The tumor volume would have been 29 mL, which would correspond to the dimension of a mean intracranial meningioma from our time (*Czarnetzki and Schwaderer, 2003, Weber et al., 2002*).

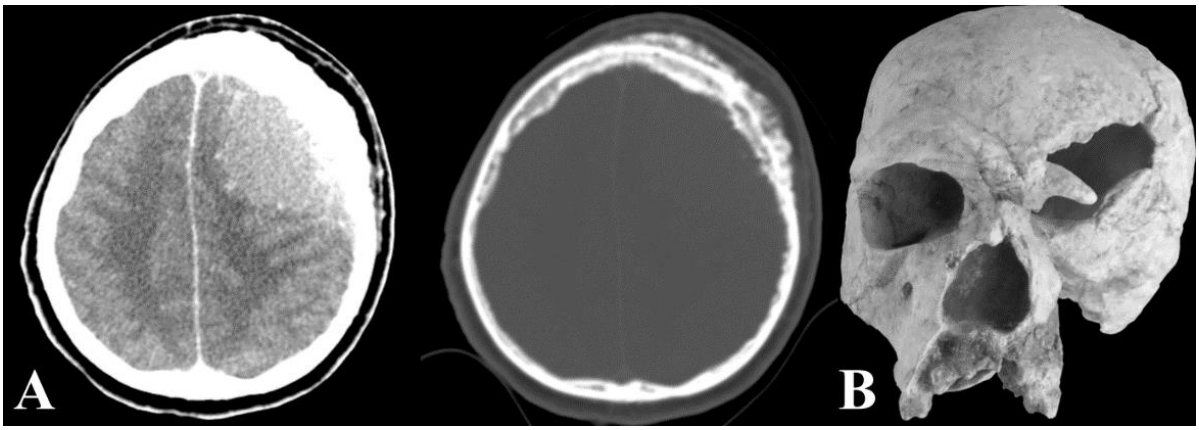


**Figure 21**. Convexity meningioma with associated hyperostosis (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*) (A). Copy of *Homo steinheimensis* cranium *(adapted, UrmenschmuseumSteinheim*) (B). (from *Cucu et al., 2019a*)

*Pharaonic meningiomas in Ancient Egypt*

When it comes to the existance of intracranial meningiomas with hyperostotic changes in ancient Egyptians, the earliest case of osseous modification of the cranium from ancient Egypt was founded at Helouan, in the period of Royal Excavations. The cranium had a osseous modifications (hyperostosis) in the right parietal region, thus demonstating the existence of a parasagittal meningioma and it belonged to the First Egypt Dynasty (*Hussein, 1951, Hussein, 1947, Rogers, 1949*). Furthermore, as regards the neurosurgical treatment of head tumors at that time, Herodotus recorded that in Egypt they were specialists in head diseases (*Herodotus, 1920, York and Steinberg, 2010*), and the treatment for these tumors was represented by paste applications on the tumor, burning with red irons, excision with a knife or leaving the swelling untreated (*David, 2008*).

*The earliest illustration of a meningioma with hyperostotic changes*

In 1730, Johann Salzmann drew the first meningioma with hyperostosis (*Salzmann, 1730a*). The tumor was a left fronto-parietal meningioma with intra-and extracranial extension (Figure 22). This case was called *"Exostosisseu ex crescentia crania osseo-spongiosa"* and was reported in *Collegium Naturae Curiosum* (*Salzmann, 1730b*), the first natural science and medical journal (*Kompanje, 2004, Okonkwo and Laws, 2009, Cucu et al., 2019a*).

Salzmann not only left us the earliest illustration of a hyperostotic meningioma, but also a meticulous course of illness of the patient, in which he specified that it lasted for over 4 years and was mainly represented by the intracranial hypertension syndrome (*Salzmann, 1730b*).

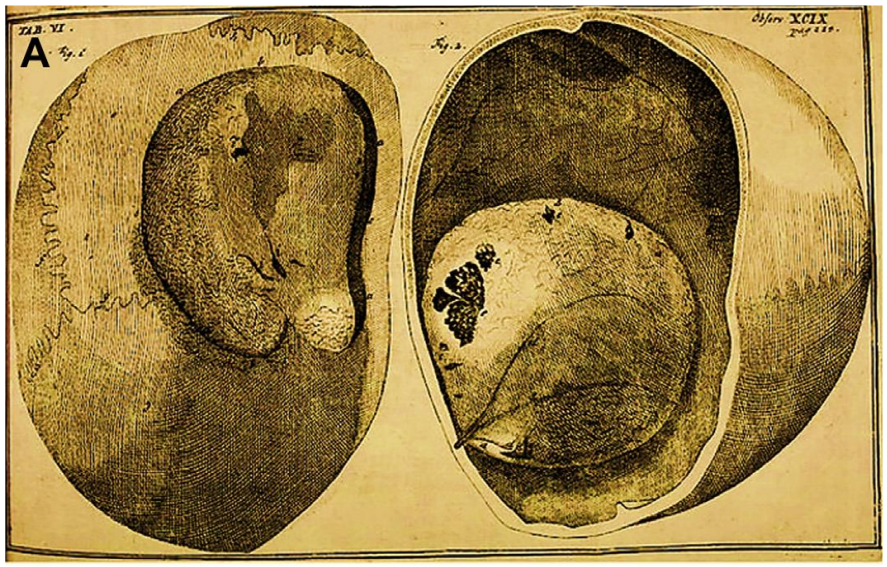


**Figure 22**. Salzmann's earliest known illustration of a hyperostotic meningioma (adapted after *Salzmann, 1730a* and *Verhoeven et al., 2019*)

*First meningioma monograph*

At the end of the French Enlightenment, in France, the surgeon Antoine Louis (1723-1792) wrote the first monograph on meningiomas (*Barthélemy et al., 2016*). Interested in brain surgery, Louis called these tumors *"fongueses de la dure-mère"* and considered them to develop from the dura mater (*Louis, 1774*).

In the monograph *"Mémoire sur les tumeurs fongueuses de la dure-mère"* printed in *"Mémoires de l'Académie Royale de Chirurgie"* in 1774 (*Al-Rodhan and Laws, 1990*), Louis reported 20 cases, some among them illustrating skull meningiomas with extracranial extension (*Louis, 1774*). When it comes to the neurosurgical treatment of these tumors, even though during Louis's time the tumors were destroyed with caustic solutions (e.g., potash), wine, herbs or rose honey, he recommended the resection of tumors which he described more throroughly in an essay published in 1774 (*Finger, 1994*).

*The most beautiful meningioma monograph illustrations*

At the beginning of the 19$^{th}$ century, the French pathologist Jean Cruveilhier (1791-1874) (Figure 23) published in *"L'Anatomie Pathologique du Corps Humain"* (*Cruveilhier, 1829*) fabulous illustrations of meningiomas with bone involvement (Figure 23).

He considered intracranial meningiomas to be cancer of the brain meninges. Cruveilhier divided them into three groups: (1) *tumors with origin in the internal layer* of the duramater that grow inside of the skull, compressing the brain, (2) *tumors with origin in the external layer* of the duramater that tend to grow toward the skull and to erode the bones of the skull and (3), *a rarer type* of meningiomas that originate in the arachnoid layer (*Berhouma, 2013, Cucu et al., 2019a*). Through his work and activity, Cruveilhier was an important pillar in the emergence of the anatomical and clinical method, especially in neurosurgical sciences (*Berhouma, 2013*).

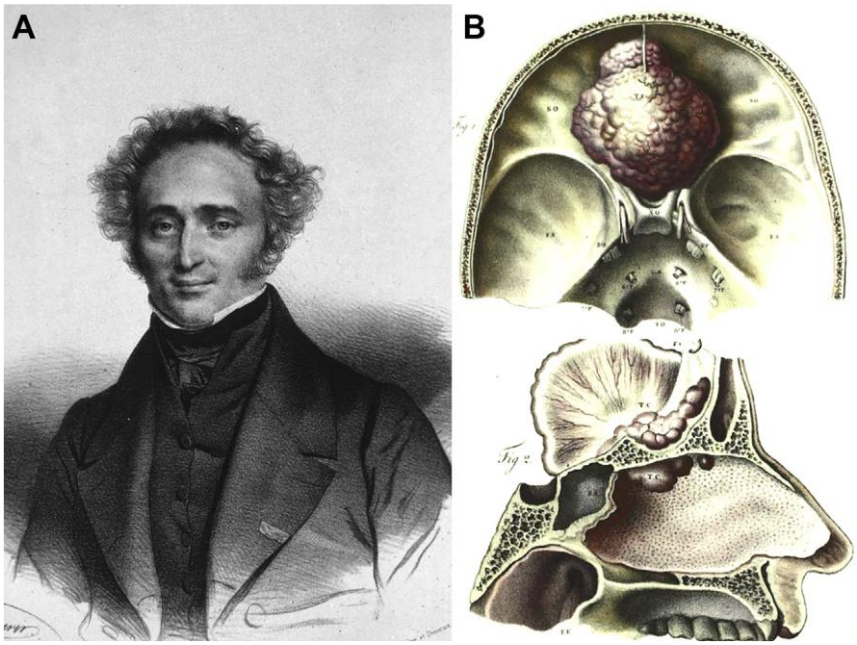


**Figure 23**. Jean Cruveilhier (A). Giant anterior cranial base meningioma eroding and invading the lamina cribrosa (B). (adapted after *Cruveilhier, 1829* and *Berhouma, 2013*)

*The first successful surgery of a meningioma*

Once with the beginning of the 19th century, the Italian school of neurosurgery started to recommend complete and prompt resection in the management of intracranial tumors (*Mastronardi and Ferrante, 2009*). Zanobi Pecchioli (1801-1866) was the first to successfully remove an intracranial meningioma (*Paterniti, 2015*), of a 45 year old man with a prolonged cephalalgia, exaggerated by the digital compression of a mass located at the level of the skull and having extracranial extension (*Al-Rodhan and Laws, 1990*, *Paterniti, 2015*). The tumor was in the right frontal area, was of important size, eroded the skull and the all tumor area was ulcerated (*Guidetti et al., 1983*). Later, in 1840, Pecchioli's explanation of this surgical intervention was chosen for the candidacy organised to occupy the Chair of Surgery from the University of Paris (*Giuffrè, 1984, Guidetti et al., 1983, Pecchioli, 1838*).

Apart from Pecchioli, the Italian Andrea Vaccà Berlinghieri (1772-1826) suggested four steps to be taken in the resection of tumors of the dura mater (e.g. *meningioma*): craniectomy of the skull with burr holes, resection with a knife of the tumor and also of the dura mater, ligation of cut vessels, as well as meningeal artery occlusion, if this was affected in the course of surgery (*Giuffrè, 1984, Guidetti et al., 1983, Mastronardi and Ferrante, 2009).*

*Research on the hyperostosis of meningioma during the birth of modern neurosurgery*

Further research regarding meningiomas with hyperostotic changes (Figure 24) was undertaken by the renowed German pathologist Rudolf L. K. Virchow (1821-1920), author of the *Omnis cellulla e cellula* theory (Figure 24). Virchow described the psammoma of the duramater (e. g. *meningioma*), localised at the cranial base and presenting exostosis of the sphenoid bone (*Virchow, 1864*) (Figure 24). According to the images he himself drew to illustrate the case, the meningioma extended to the midline, and the bony exostosis of the sphenoid bone had reached important sizes (*Alpers and Harrow, 1932, Virchow, 1864*).

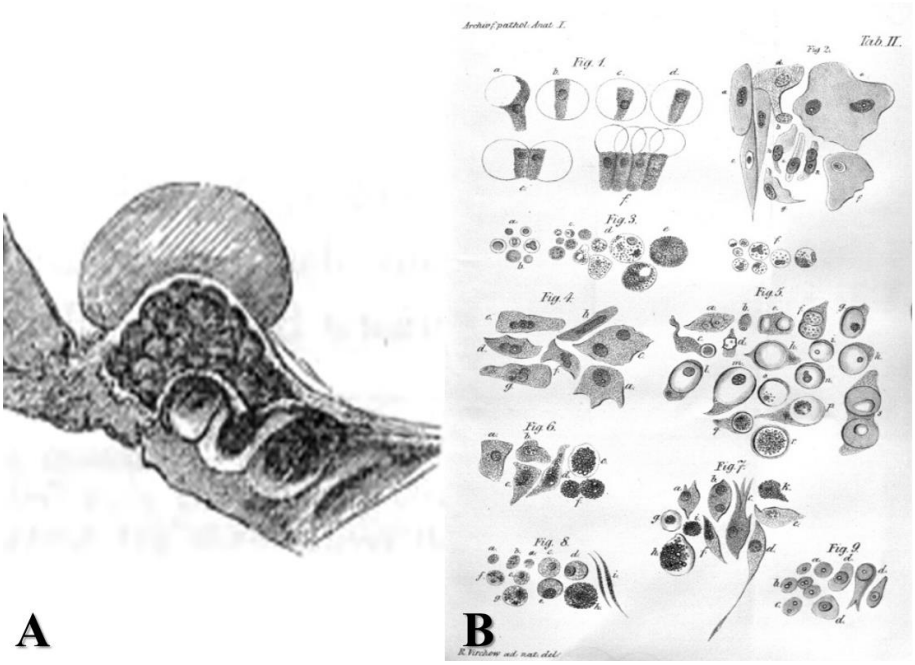


**Figure 24**. Illustration of Rudolf Virchow's case of cranial base meningioma with exostosis (adapted after *Virchow, 1864*) (A). Illustration of Virchow's cell theory *Omnis cellulla e cellula* (from *Archiv für Pathologische Anatomie und Physiologie, 1847*) (B). (public domain)

The first case of meningioma with hyperostotic changes reported in detail was Spiller's, in 1899, and was exposed at the Meeting of the Section on General Medicine of the College of Physicians of Philadelphia and published in *The Medical Record*: *"the case was that of a man who, sixteen years previously, had fallen and injured the left side of his head. After eight years a swelling was noticed in this situation, and several years later paresis in the right lower extremity, and later in the right upper extremity also. Headache and vomiting were superadded, speech became paraphasic, and a convulsion occurred. On ophthalmoscopic examination bilateral optic neuritis was found. Operation was decided upon; a segment of greatly thickened and infiltrated bone was removed from the calvarium, and a new growth found in the cortex of the left motor area. Hemorrhage was profuse and death occurred a few hours after the operation from loss of blood and shock. On histologic examination the growth was shown to be an endothelioma [meningioma]"* (*Spiller, 1899*).

*Harvey Williams Cushing, The Father of Meningiomas*

H. W. Cushing (1869-1939) (Figure 25) was also interested in the mechanism of hyperostosis, reporting a series of 20 cases of meningioma with bone involvement, remaining in the history of neurosurgery as the first to describe the interaction between meningiomas and bone (*Di Cristofori et al., 2018*) (Figure 26). He noticed that meningioma cells were found in regions with bone involvement, reporting that hyperostosis was much more common in meningiomas *en plaques* than in meningioma *en masse* (*Cushing, 1922*).

Another one of Cushing's theories was that tumor cells of meningioma were forced into the bone canaliculi by increased intracranial pressure: "*under the influence of intracranial pressure, the*

*tumor cells become crowded into and through the vascular dural spaces, and finally into the canaliculi of the bone. As a consequence, the bone becomes rough, with subsequent osteoblastic proliferation which causes hyperostosis. There can be little doubt that the thickening occurs in this way, but intracranial pressure may have nothing to do with it, in view of the fact that the flat endotheliomas [meningiomas] which do not increase pressure are, as we have seen, those which most often tend to invade the bone*." (*Cushing, 1922*).

**Figure 25**. Photograph of Harvey Cushing, taken in 1900 or 1901. (public domain)

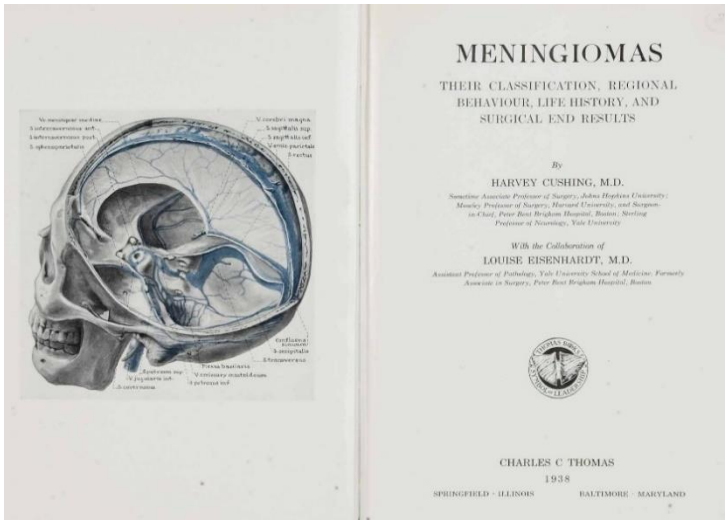


**Figure 26**. The book of H. Cushing and L.C. Eisenhardt: *Meningiomas. Their classification, regional behaviour, life history and surgical end results* (1938), first edition (public domain)

Several years after Cushing, Phemister and Penfield also undertook research on hyperostosis from meningiomas (*Phemister, 1923, Penfield, 1923*), and in 1972 Grant resected first the frontal hyperostosis of a bilateral parasagittal *en plaque* meningioma (*Black, 1999, Laws Jr., 1999*).

At the beginning of the 20$^{th}$ century, more investigators following the hyperostosis associated with some meningiomas reached different conclusions. Thus, some authors reported that hyperostosis was a manifestation of meningioma invasion (*Bonnal et al., 1980, Cushing, 1922, Derome and Guiot, 1978, Pieper et al, 1999*), while others considered that these bony changes were in fact only reactionary osseous changes (*Heick et al., 1993, Landow et al., 1942*). Moreover, other authors also took into consideration the existence of a neuropeptide serotonine influencing bone metabolism (*Oury et al., 2010, Yadav and Ducy, 2010*), somatostatin receptor 2A expression (*Matschke et al, 2011*) or insulin-like growth factor 1 and osteoprotegerin (*Di Cristofori et al., 2018*) in the attempt to explin bone hyperostosis in intracranial meningiomas.

***Conclusions***

Even though the exact molecular mechanisms of hyperostosis in intracranial meningiomas are not yet fully known and whether osteosynthesis or osteolysis processes are involved or not, the contributions of neurosurgeons and neuropathologists over the time remain of major importance in the development of both neurosurgery and neurooncology, as well as of neurosurgical techniques,

and especially skull base approaches (*Cucu et al., 2019a*).

### I.2.2. Neurosurgical research on primary brain tumors

#### I.2.2.1. Evidences on the value silver nitrate staining in the diagnosis of cerebral astrocytic tumors

***Background***

The diagnosis of a brain tumor involves a large multidisciplinary context, established by a team of neurosurgeons, neuroradiologists, neuropathologists and neurooncologists (*Turliuc et al. 2007*). Therefore, precise hystopathological diagnosis to improve the treatment and the further prognosis is a *sine qua non* condition in the treatment of a brain tumor.

In many cases, in the neurosurgery services, the anatomopathologist finds himself frequently in difficulty in the case of a brain biopsy, especially when it comes from the periphery of an astrocytic tumor and is small in size, and the neurosurgeon requires the immediate differentiation between a low-grade astrocytoma and a reactive gliosis. For this reason, it is necessary to discuss the case beforehand within the complex team above-mentioned, with the mandatory participation of the anatomopathologist. This way, the neurosurgical intervention and the anatomo-pathological processing and interpretation of the samples can be planned. The purpose of this collaboration is represented by the need to obtain tissue for cell cultures or special fixation techniques (*Esiri and Oppenheimer, 1989, McKeever and Blaivas, 1989*).

In order to establish an accurate histopathological diagnosis, both during the intervention as well as subsequently, the neuropathologist must examine the neurosurgical drawings and to be familiar with the history of the disease, the clinical and imaging aspects of the case in study. Moreover, the neuropathologist must understand the surgical procedure very well (Figure 27 and 28).

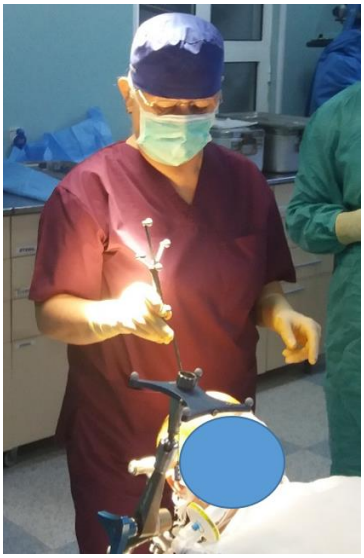

**Figure 27**. Preoperative neuronavigation aspects in brain tumor surgery (*Assoc. Prof. Dr. M.D. Turliuc's personal collection*)

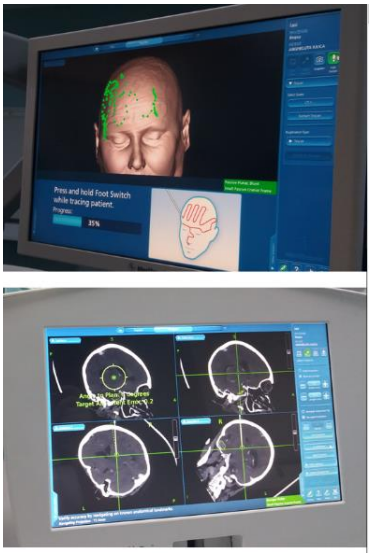

**Figure 28**. Neuronavigation system for image-guided brain surgery (*Assoc. Prof. Dr. M.D. Turliuc's personal collection*)

In the practice of neurosurgery and especially in the field of brain cancers, it is very important to know the grade of brain tumors, particularly of gliomas, due to the fact that they are the most common primary malignant brain tumors in adults and represent 81% of malignant brain tumors (*Ostrom et al., 2014*). Among them, astrocytomas represent 75% of all gliomas (*Grier and Batchelor, 2006*).

The growth potential of the tumor is achieved nowdays through current immunohistochemical methods, but there are many other cell cycle molecules that can be used for the histochemistry evaluation of cell proliferation, with a major importance in the field of neurooncology.

The metaphase Nucleolar Organizer Regions (NORs) are loops or chromosomal segments which contain ribosomal genes, and these genes are clustered in thr chromosomes 22, 21, 15, 14 and 13. Moreover, the transcriptional activity of these segments localized intranuclearly plays a very important role in nucleoli forming, directing the ribosome syntesis and associated proteins (*Crocker and Murray, 2003*). C23 (nucleolin) and B23 (nucleophosim), NORs associated protein are selectively stained by silver impregnation technique. After silver-staining, the NORs can be identified as black dots that are localized throughout the nucleolar area, and are called AgNORs (*Dumitrescu et al., 2010a*) (Figure 29 and 30).

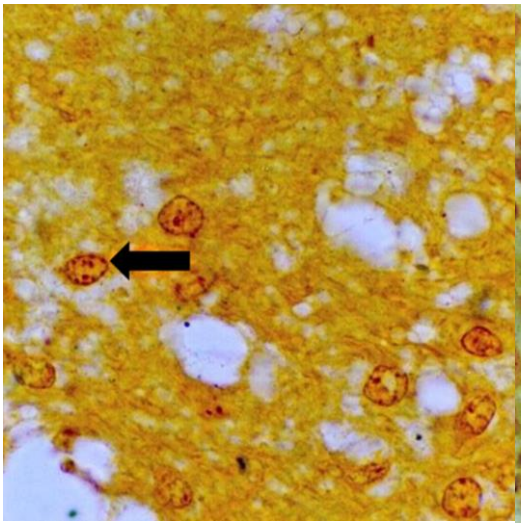

**Figure 29**. Grade II astrocytoma: 1 to 5 small black dots in tumor cell nuclei (silver impregnation method, x1000). *Courtesy of Dr. G. F. Dumitrescu* (from *Dumitrescu et al., 2010a*)

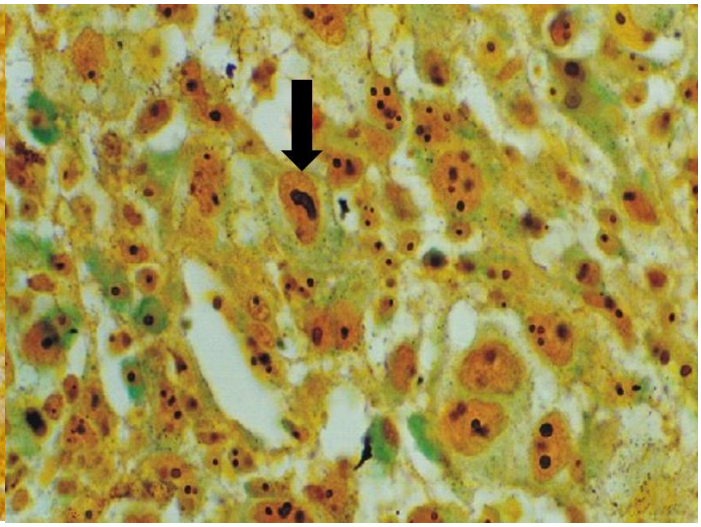

**Figure 30**. Grade IV astrocytoma: tumoral nuclei with 2 to 7 medium black dots scattered across nucleus area; one nucleus with great AgNOR dot (black arrow) (silver impregnation method, x1000). *Courtesy of Dr. G. F. Dumitrescu* (from *Dumitrescu et al., 2010a*)

The expression of AgNOR proteins are associated with biological properties of tumoral cells: rapidity of cellular proliferation, histological grade of differentiation, DNA content and metabolic activity (*Derenzini and Trerè, 2001, Pich et al., 2000, Ploton et al., 1992, Trerè, 2000*). Even though over the last 20 years more than 400 studies have been carried out in an attempt to find a correlation between AgNORs'quantity and quality with rapidity of proliferation and tumor aggressivness (*Crocker and Murray, 2003, Jham et al., 2017*) and AgNOR determination was used in

oncopathology as a bioparameter to differentiate malignant cells from benign or even normal cells (*Elangovan et al., 2008, Eslami et al., 2005, Giuffrè et al., 2008*), the precise significance of AgNORs proteins is not fully understood.

Due to the fewer number of articles about AgNORs expression in astrocytomas and because evaluation of AgNORs represents a good alternative approach to assess the tumor growth fraction, in this study we have analyzed a possible link between AgNOR's morphology and AgNOR's number with histopathological tumor subtype (*Dumitrescu et al., 2010a*).

*Paper published in this field:*

**Turliuc D**, Dumitrescu GF, Indrei A. *Colaborarea neurochirurg-neuropatolog in diagnosticarea tumorilor cerebrale.* Revista Medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi 2007, 3(3):649-657.

Dumitrescu GF, Indrei A, Poeata I, Haba D, Agrigoroae E, Grămadă F, **Turliuc DM**. *Diagnostic value of silver nitrate staining for nucleolar organizer regions in cerebral astrocytic tumors*. Romanian Neurosurgery 2010, 17(1):64-72.

*This article has 1 ISI citation and a total of 3 citations.*

***Material and methods***

The study was conducted in the Department of Neurosurgery within *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași, where 16 primary cerebral astrocytic tumors were retrospectively identified and then stereotactic biopsied and pathologically diagnosed (Figure 31 and 32). According to the standard procedure, all 16 cases of tumor samples were fixed in 10% buffered formalin, included in paraffin and then stained with HE. All cases were diagnosed and graded according to the WHO Classification of Brain Tumors (*Kleihues and Cavenee, 2000*) and classified into 3 groups: 4 cases of diffuse astrocytoma, 4 cases of anaplastic astrocytoma and 8 cases of glioblastoma multiforme (4 cases with small cells and 4 cases with giant cells) (*Dumitrescu et al., 2010a*).

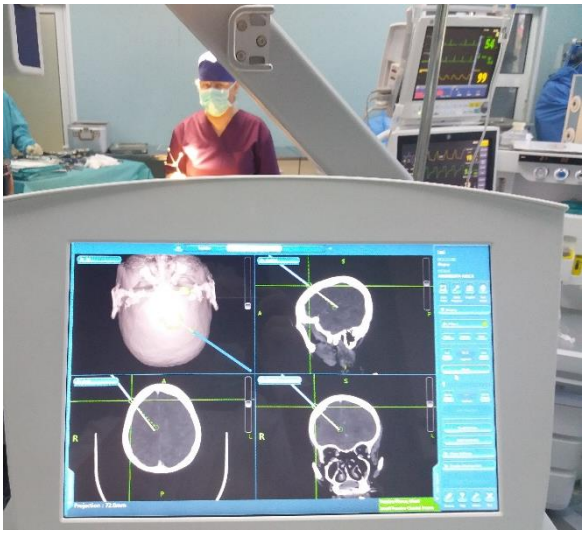

**Figure 31**. Image from preoperative planning in the case of a tumor biopsy (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

**Figure 32**. Intraoperative images of stereotactic guided biopsy (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

***Results***

When it comes to the results obtained, the average values of mean AgNORs/nucleus for each astrocytic tumor and its correlation with the malignant degree are shown in Table 12. Considering both vascular and tumoral cells, the mean values of mAgNORs/nucleus had a trend of linear increase, as the malignancy of the tumor increases, from 1.96 for grade II astrocitomas, 2.34 for grade III astrocitomas, to 3.18 for grade IV astrocitomas (*Dumitrescu et al., 2010a*).

**Table 12**. Mean values of AgNORs in tumoral and vascular nuclei of astrocytomas according to their malignancy grades (from *Dumitrescu et al., 2010a*)

| MALIGNANCY GRADE | AVERAGE NUMBER OF AgNORs/NUCLEUS | | | | | |
|---|---|---|---|---|---|---|
| | tumoral cells | | vascular cells | | Whole tumor | |
| | Range | Group mean | Range | Group mean | Range | Group mean±SD |
| Diffuse astrocytoma (G II) | 2.14<br>2.26<br>2.31<br>2.38 | 2.27 | 1.43<br>1.45<br>1.53<br>1.54 | 1.52 | 1.78<br>1.92<br>1.96<br>2.18 | 1.96 |
| Anaplastic astrocytoma (G III) | 2.63<br>2.74<br>2.85<br>2.91 | 2.78 | 1.82<br>1.82<br>1.98<br>1.99 | 1.90 | 2.28<br>2.30<br>2.36<br>2.42 | 2.34 |
| Glioblastoma multiforme (G IV) | 2.47<br>2.68<br>2.79<br>3.12<br>3.76<br>3.83<br>4.02<br>4.15 | 3.35 | 2.54<br>2.72<br>2.72<br>3.60<br>2.77<br>2.86<br>3.04<br>4.00 | 3.03 | 2.50<br>2.75<br>2.92<br>3.14<br>3.34<br>3.59<br>3.39<br>3.88 | 3.18 |

Our study has highlighted a difference between giant and small cells subtypes, as giant cells glioblastoma expressed higher values (3.94) than small cells glioblastoma (2.76) in terms of correlation between mAgNORs/tumoral nucleus and histopathological type of glioblastoma multiforme (Table 13). Because the mean values of mAgNORs/tumoral nucleus were almost identical (2.78 and 2.76 respectively), histological differential diagnosis between small cells glioblastomas and anaplastic astrocytomas has proven to be difficult to be determined solely on the basis of this ratio (*Dumitrescu et al., 2010a*).

**Table 13**. Histopathological differential diagnosis between anaplastic astrocytoma and glioblastoma according to mAgNOR/tumoral nucleus and mAgNOR/vascular nucleus (from *Dumitrescu et al., 2010a*)

| NUMBER of AgNORs/ NUCLEUS | HISTOLOGICAL SUBTYPE | | | | | |
|---|---|---|---|---|---|---|
| | Anaplastic astrocytoma | | Small cells glioblastoma | | Giant cell glioblastoma | |
| | Range | Mean | Range | Mean | Range | Mean |
| mAgNOR/ tumoral nucleus | 2.63<br>2.74<br>2.85<br>2.91 | 2.78 | 2.47<br>2.68<br>2.79<br>3.12 | 2.76 | 3.76<br>3.83<br>4.02<br>4.15 | 3.94 |
| mAgNOR/ vascular nucleus | 1.82<br>1.82<br>1.98<br>1.99 | 1.90 | 2.54<br>2.72<br>2.72<br>3.60 | 2.895 | 2.77<br>2.86<br>3.04<br>4.00 | 3.167 |

***Discussions***

The aim of this study was to determine the AgNORs utility in the histopathological differentiation of malignancy grades of astrocytomas. Within each histopathological subtypes we found a large range of AgNORs values, this highlighting the morphological heterogeneity and variations in behavior of astrocytic tumors. Nonetheless, we could say that there is a linear correlation between histopathological subtypes and mean values of AgNOR/nucles (*Dumitrescu et al., 2010a*).

By comparing the data in the literature with the data obtained in our study on the mean number of AgNORs in astrocytic tumors, we noticed that the average values of AgNORs we obtained are in agreement with previous studies (Table 14). Moreover, in a more recent study, from 2017, carried out on sixty patients of whom 49 had astrocytic tumors, Jham *et al.* also demonstrated that AgNOR markers can be used to predict proliferative potential of astrocytic tumor and can be used as additional method of diagnosis alongside with conventional histopathological diagnosis (*Jham et al., 2017*).

**Table 14**. Comparison between the main studies in the literature on average values of AgNORs/nucleus and the current report (from *Dumitrescu et al., 2010a*)

| | Mean number of AgNORs/nucleus | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Author | **Diffuse astrocytoma (Grade II)** | | | **Anaplastic astrocytoma (Grade III)** | | | **Glioblastoma multiforme (Grade IV)** | | |
| | tumoral nucleus | vascular nucleus | nucleus | tumoral nucleus | vascular nucleus | nucleus | tumoral nucleus | vascular nucleus | nucleus |
| *Jham et al., 2018* | 1.92±0.41 | | | 2.77±0.38 | | | 3.42±0.31 | | |
| *Janczukowicz, 2003* | | | 1.65 | | | 2.11 | | | 2.55 |
| *Choi et al., 1997* | | | 1.2±0.26 | | | 1.90±0.64 | | | 1.96±0.57 |
| *Hara et al., 1991* | 1.52±0.07 | 1.80±0.13 | | 1.98±0.23 | 2.87±0.50 | | 2.05±0.29 | 3.13±1.13 | |
| *Tokunaga et al., 1997* | | | 2.04±0.54 | | | 2.40±0.77 | | | 2.71±1.13 |
| *Haberland et al., 1996* | | | 1.73 | | | 2.81 | | | 4.56 |
| *Tokiyoshi et al., 1992* | | | 1.68±0.87 | | | 1.85±1.03 | | | 2.76±1.26 |
| *Pedal et al., 1994* | | | 1.98 | | | 2.84 | | | Small cells GM:3.33 Giant cells GM: 4.24 |
| Present study | 2.27 | 1.52 | 1.96 | 2.78 | 1.90 | 2.34 | 3.35 | 3.03 | 3.18 |

All the authors in the studies presented have obtained a gradual increase spectrum of the average number of AgNOR from grade II and III astrocytomas, to grade III astrocytomas, concluding that the number of AgNORs reflects the degree of malignancy in these types of brain cancers (*Choi et., 1997, Haberland et al., 1996, Hara et al., 1991, Janczukowicz, 2003, Jham et al., 2017, Pedal et al., 1994, Tokiyoshi et al., 1992, Tokunaga et al., 1997*).

Moreover, in this study we observed that the outliers values of the average number of AgNOR/tumoral nucleus between grade III astrocytomas and grade IV astrocytomas (small cells glioblastoms) overlap, probably due to the fact that while some of the anaplastic astrocytomas considered samples, they actually represented infiltration regions of a glioblastoma, the sample was too small and had no necrosis or vessel to be visible. Consequently, AgNOR determination could be considered as being useful in biopsies and in small specimens from the infiltrating tumor margins, where the usual histopathological characteristics of malignancy may be absent (*Dumitrescu et al., 2010a*).

***Conclusions***

In our study, through the results achieved, we could conclude that the proliferative processes of tumor cells and vascular cells are closely related, given the fact that we found an increased average number of mAgNOR/vascular nucleus in grade III and IV astrocytomas.

Furthermore, as the proliferative activity both in tumoral and vascular tumoral cells of the

astrocytic tumours was enhanced with increasing histopathological grade, we believe, based on our study, that the AgNORs is a useful marker in evaluating the degree of malignancy in cerebral astrocytomas, as it supplements the information obtained with conventional histological assessment (*Dumitrescu et al.,2010a*).

### I.2.3. Research on the cerebral metastasis: case studies and literature review

***Background regarding brain metastasis***

Approximately 20% of all patients with cancer will develop brain metastasis, and even if any type of neoplasia can metastasize to the brain, the most common ones come from lung, colorectal cancer, breast cancer, renal cell carcinom or melanoma (*Barnholtz-Sloan, et al., 2004, Nayak et al., 2012, Tabouret et al., 2012*). Moreover, according to necropsy studies, the incidence of these brain metastasis would be up to 40% (*Percy, 1970, Posner and Chernik, 1978, Tsukada et al., 1983*).

Unfortunately, these brain metastasis remains a significant cause of the increase of overall cancer mortality, given that the prognosis is poor in spite of the modern multimodal treatments represented by brain surgery, radio-, immuno- and chemotherapy. Nonetheless, current studies are focusing on the patient survival, the risks of treatment and long-term toxicities (*Achrol et al., 2019*).

In recent years, new techniques have emerged in neurosurgery regarding the treatment of brain metastasis that no longer require classic craniotomy: stereotactic laser ablation, convection-enhanced delivery and focused ultrasound (*Achrol et al., 2019, Ali et al., 2016, Ahluwalia et al., 2018, Rennert et al., 2018*).

***Background regarding choroidal metastasis***

Choroidal metastasis is currently a controversial topic. Even if, over the last three decades, the scientific papers treating this pathology increased, the information is sometimes contradictory (*Turliuc et al., 2015*), the frequency of this pathology ranging from 2 to 9% (*Albert et al., 1967, Kreusel et al., 2002*). Choroidal metastasis from lungs are rarer and appear in the final stages of the cancer, when the average life expectancy is lower than 6 months (*Arevalo et al., 2005, Asteriou et al., 2010*). Furthermore, when they are identified, at least two organs usually have metastasis (*Shields and Shields, 2008*).

*An extremely rare case of choroidal metastasis which we have treated in our department has been published in a journal indexed in ISI Web of Science and summary of the most important data are presented here, in the followings:*

**Turliuc D**, Sava A, Dumitrescu GF, Cucu A, Esanu A, Tudorache C, Costache II, Costea CF. *Right visual loss due to choroidal metastasis of a papillary adenocarcinoma of the lung*, *Case report*. Rom J Morphol Embryol 2015, 56(3):1173-1177. (Impact Factor in 2015 = 0.811)

*This article has 15 ISI citations and a total of 23 citations.*

***Case presentation***

In 2015 we have reported the case of a 40 year old male patient, a smoker, who was admitted

to the Department of Neurosurgery of *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital for headache, right motor deficit and visual loss of right eye. Chest CT scan highlighted a tumor located in the lower pulmonary lobe, and the cytopathology examination of bronchial brushing specimens performed at the Hospital for Lung Diseases a week previously had revealed a non-small-cell lung carcinoma (Figure 33). The ophthalmological exam revealed no light perception of the right eye with serous retinal detachment. Moreover, slit lamp exam of the right eye showed a grayish aspect of the pupil (Figure 34). Head CT scan with contrast highlighted multiple supratentorial metastasis in the left hemisphere, one of which was larger, located in the left rolandic region (Figure 35), and also another lesion in the right eyeball posterior pole (Figure 36). After surgical resection of the left rolandic lesion, the tissue obtained was processed by the usual histopathological technique and the final pathological exam revealed the diagnosis of brain metastasis of a bronchopulmonary papillary adenocarcinoma (Figure 37).

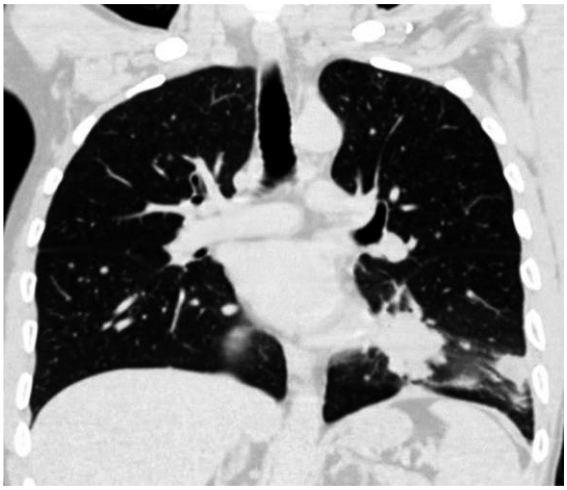

**Figure 33**. Chest contrast CT scan showing the tumor in the left lung (from *Turliuc et al., 2015*)

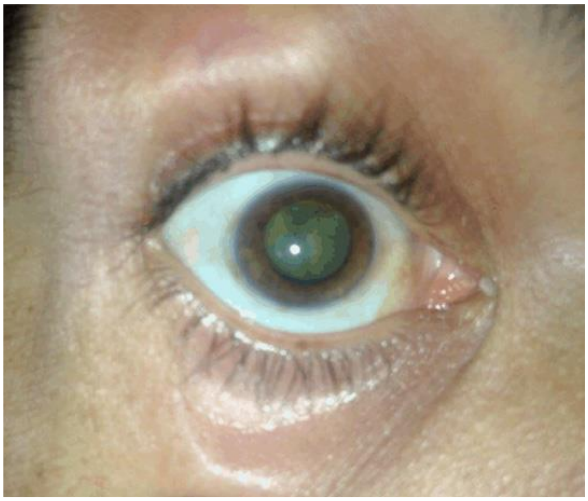

**Figure 34**. Right eye: greyish appearance of the pupil (serous retinal detachment) (from *Turliuc et al., 2015*).

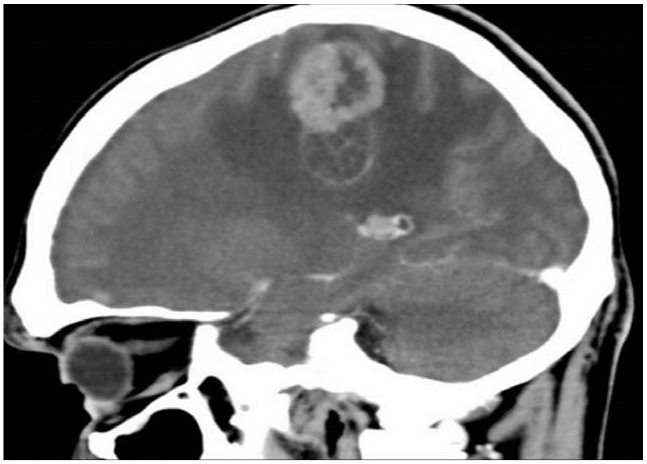

**Figure 35**. Head CT scan with contrast showing the parenchymal metastasis (from *Turliuc et al., 2015*)

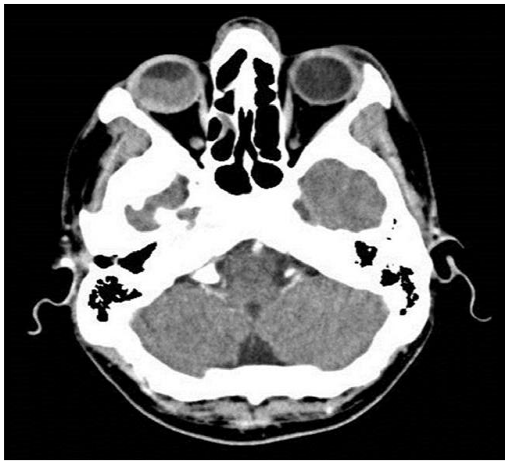

**Figure 36**. Axial contrast CT scan showing intense enhancement in right eye in close relation to the choroid (from *Turliuc et al., 2015*)

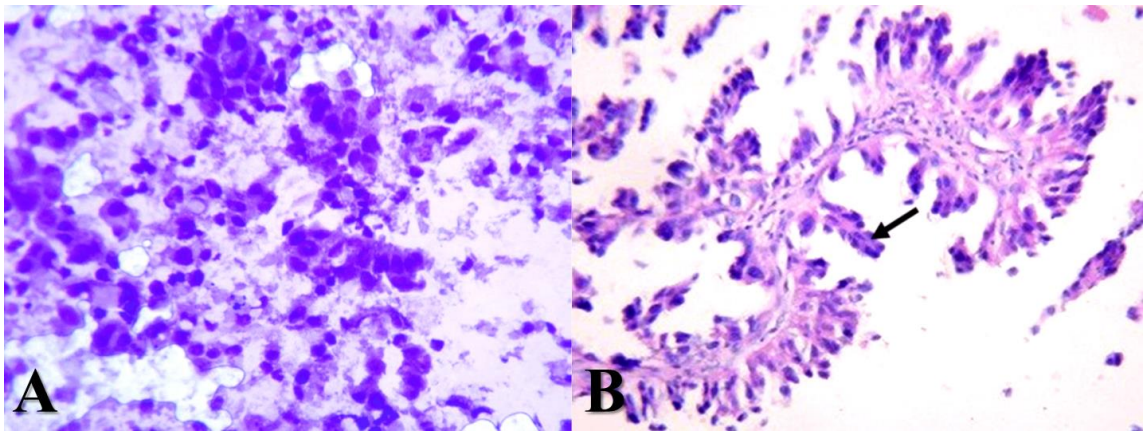


**Figure 37**. An intraoperative imprint taken from left rolandic tumor revealed nests of malignant epithelial cells (toluidine blue staining, x400) (A). High-power photomicrograph of left rolandic lesion: micropapillary features lacking fibrovascular core (black arrow) (HE staining, x400) (B) (from *Turliuc et al., 2015*)

***Discussion***

In Romania, choroidal metastasis is a rare entity, only three articles having been published so far by Romanian authors in the literature (*Fumarel et al., 2008, Munteanu et al., 2013, Munteanu et al., 1994*). Regarding the diagnosis, head CT scan is recommended, given the fact that 22% of the cases of ocular metastasis are combined with cerebral metastasis (*Mewis and Young, 1982*). In our patient's case, the CT scan revealed multiple supratentorial metastasis in the left hemisphere, one of which of larger sizes, located in the left rolandic region, which was completely resected. Unfortunately, the presence of choroidal metastasis is a sign of poor prognosis, indicating the end-stage of lung cancer (*Aragão et al., 2013, Asteriou et al., 2010*).

The treatment of intraocular metastasis depends very much on the Karnofsky Performance Scale Index and is unfortunately palliative, consisting in exenteration, enucleation, chemotherapy or orbital irradiation (*Asteriou et al., 2010, Dobrowsky, 1988*).

***Conclusions***

Choroidal metastasis from a bronchopulmonary cancer is uncommon in our region, and the diagnosis and treatment of these lesions require an interdisciplinary collaboration between pneumologist, ophthalmologist, neurosurgeon, radiologist, anatomopathologist and oncologist. We are highlighting once more the importance of ophthalmological screenings of patients with brain metastasis (*Turliuc et al., 2015*).

***Background regarding Meckel's cave tumors***

The tumors located at the level of Meckel's cavum are extremely rare and represent approximatively 0.5% of all intracranial tumors (*Beck and Menezes, 1987*), the most common primary tumors located at this level being the trigeminal schwannomas and meningiomas (*Nemzek et al., 1996, Sawaya, 2004*). Although metastasis from various cancers can develop at the level of the trigeminal nerve (*Theuer et al., 2007*), metastasis of colon adenocarcinoma are extremely rare, the

literature reporting only three such cases (*Mastronardi et al., 1997, Nair et al., 2015, Naphade and Keraliya, 2013*).

*An extremely rare case of Meckel's cave metastasis was published in a journal indexed in ISI Web of Science and summary of the most important data are presented here, in the followings:*

**Turliuc DM**, Cucu AI, Costan VV, Costea CF. *Rare etiology of trigeminal nerve neuralgia – metastatic adenocarcinoma of the colon*. Romanian Journal of Oral Rehabilitation 2016, 8(2):40-43.

*This article has 2 ISI citations and a total of 3 citations.*

***Case presentation***

We are reporting the case of an elderly patient, 70 years old, admitted to the Department of Neurosurgery of *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital of Iași for right trigeminal neuralgia. The MRI scan reveald an increase in the size of the right cavernous sinus (Figure 38). The biopsy of the lesion established the diagnosis of metastatic adenocarcinoma of the colon and the patient underwent radiosurgical treatment without reducing of the symptoms (*Turliuc et al., 2016*).

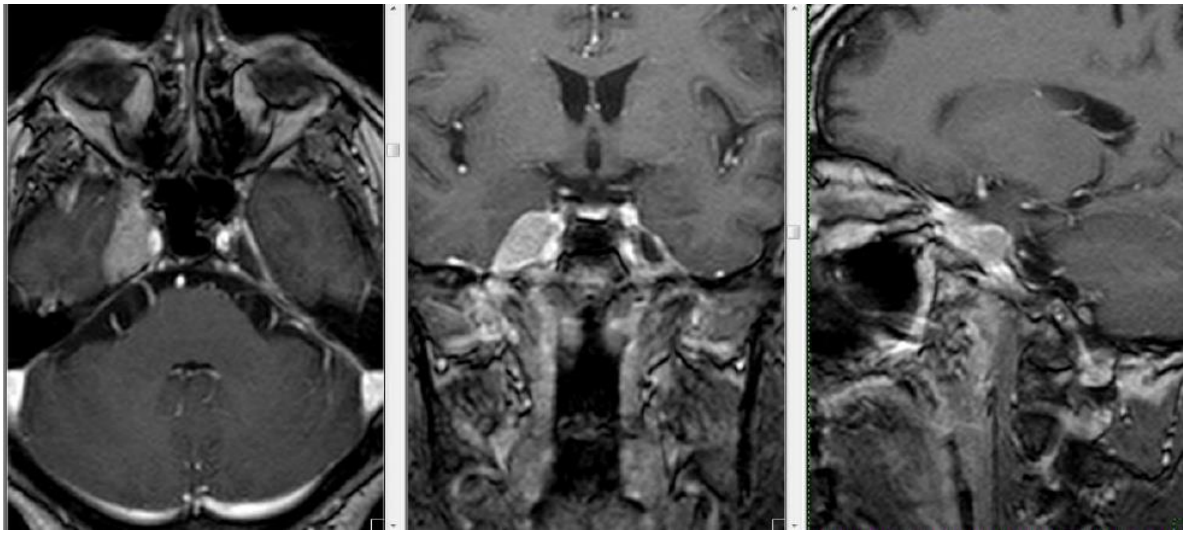

**Figure 38**. T1WI axial gadolinium-enhanced MRI images (axial, coronal, sagittal) after eight months, showing enlargement of the right cavernous sinus (from *Turliuc et al., 2016*)

Metastasizing of the Gasserian ganglion could occur: (1) through hematogenous spread from the extracranial sources, (2) by continued invasion from the extracranial tumours or (3) through cerebrospinal fluid (*Albayram et al., 2004*). The treatment of metastasis located at this level consists in radiosurgery, radiofrequency, electrocoagulation or needle rhizotomy (*Brisman, 2004, Brisman, 1989*). Even though the most common among these is radiosurgery, in the case of skull base metastasis, the percentage of symptomatology relief is of 30% (*Vikram and Chu, 1979*). Furthermore, the cranial nerves in the cavernous sinus can tolerate an irradiation dose between 30 and 40 Gy (*Leber et al., 1998*, *Tisher et al., 1993*).

To conclude, even if the most common tumors of the trigeminal nerve are schwannoma and

meningioma, this nerve could be the site of metastasis of a cancer with extracranial localization. Thus, despite the rarity of this type of metastasis, differential treatment must be considered in any type of lesion located at the level of Meckel's cave (*Turliuc et al., 2016*).

### I.2.4. Researches on the treatment of brain tumors

*Paper published in this field:*

**Turliuc MD**, Cucu AI, Costachescu B, Tudor RM, Papacocea T, Bogdanici CM, Carauleanu A, Floria M, Tanase DM, Costea CF. *The use of mannitol in neurosurgery and neuro-ophthalmology.* Cellulose Chemistry and Technology 2019, 53(7-8):625-633. (Impact Factor in 2018 = 0.857)

**Turliuc MD**, Cucu AI, Carauleanu A, Costea CF. *Efficiency and safety of microporous polysaccharide hemispheres from potato starch in brain surgery.* Cellulose Chemistry and Technology 2018, 52(7-8):505-513. (Impact Factor in 2018 = 0.857)

*This article has 2 ISI citations.*

#### I.2.4.1. The benefit of mannitol in the treatment of cerebral tumors

Mannitol began to be widely used in medicine as far back as 1940 for the assessment of the glomerular filtration rate (*Smith et al., 1940*). Later, in 1960, it was used as a hypertonic solution for the treatment of intracranial hypertension (IH) (*Fandino, 2017*), being included in the WHO model list essential medicines (**WHO Model List of Essential Medicines, 2015*) (Table 15).

**Table 15.** Physical and pharmacokinetic properties of mannitol (*Grembecka, 2018, Nissenson et al., 1979, Better et al., 2008, Lin et al.2015, De Cock, 2012., Zacharis, 2012*)

| Characteristic | Description |
|---|---|
| Molecular weight | 182 Daltons |
| Osmolarity (20%) | 1098mOsm/L |
| Volume of distribution | 0.471 L/kg |
| Onset | about 15 min |
| Maximal effect | about 45 min |
| Duration | about 6 h |
| Half-life | 70-100 min |
| Biotransformation | None |
| Excretion | Renal |
| Reabsorption | 7% |
| Sweetness[a] | 0.5-0.7 |
| Caloric value [kcal/g] (EU) | 2.4 |
| Heat of solution | -29 |
| Viscosity at 25 °C | low |
| Hygroscopicity | low |

[a]sucrose sweetness = 1

In neurosurgery, mannitol is used to lower intracranial pressure (ICP) elevation (Class II) (*Bratton et al., 2007*), being also suggested in acute IH when transtentorial herniation (Class III) occur (*Bratton et al., 2007*, *Wakai et al., 2007*).

Mannitol is also considered as the primary management for the control of IH caused by cerebral edema in patients with tumors, strokes, head injuries or subarachnoid hemorrhage (*Papangelou et al., 2009*). Nevertheless, there is no evidence in the literature of the optimal dose or duration of treatment (*Sorani et al., 2008*), and no ICP threshold over which mannitol administration is recommended has been established. The peak ICP effect of mannitol occurs after 30-45 minutes and lasts for 6 to 9 hours, and 20% of the intravenous solution at a dose of 0.15-0.20g/kg over 30-60 minutes is considered to be secure (*Better et al., 1997, *EFSA, 2011, Flynn, 2007*) (Table 16).

**Table 16**. Mannitol and different concentrations of hypertonic saline (*Freeman and Welbourne, 2018*)

| Solution | Sodium concentration (mmol $L^{-1}$) | Osmolarity (mOsm $L^{-1}$) | Equiosmolar dose mL (275 mOsm) | Dose (mL $kg^{-1}$) for 80 kg person |
|---|---|---|---|---|
| NaCl 0.9% | 154 | 308 | 892 | 11 |
| Ringer's lactate | 130 | 275 | 1000 | 12.5 |
| Saline 1.7% | 291 | 582 | 472 | 5.9 |
| Saline 3% | 513 | 1027 | 268 | 3.4 |
| Saline 5% | 856 | 1711 | 161 | 2 |
| Saline 7.5% | 1283 | 2566 | 107 | 1.3 |
| Saline 10% | 1712 | 3424 | 80 | 1 |
| Saline 30% | 5000 | 10.000 | 27.5 | 0.34 |
| Mannitol 10% (1 g $mL^{-1}$) | | 549 | 502 | 6.3 |
| Mannitol 20% (2 g $mL^{-1}$) | | 1098 | 251 | 3.1 |

Regarding the side effects, mannitol repeated administration can lead to the occurence of a *rebound phenomenon*, in which ICP elevation can occur, various authors having tried to explain this phenomenon through the fact that the osmotic agent leaks into the damaged cerebral parenchyma across a injured blood-brain barrier, and this mannitol accumulation in extracellular fluid is pulling water with it (*Davis and Lucatorto, 1994, Shawkat et al., 2012, Troupp et al., 1971*). Moreover, Sankar *et al*. have proven this mannitol accumulation in an intracranial meningioma with magnetic resonance spectroscopy (*Sankar et al., 2008*). Other side effects of mannitol administration include: electrolyte abnormalities (most commonly hyperkaliemia) (*Preston et al., 1998, Kaye and Grogono, 2000*) severe dehydration, progressive hyperosmolarity (*Kaneda et al., 2010*), hypersensitivity reactions or cardiopulmonary edema (*Davis and Lucatorto, 1994, Troupp et al., 1971*) and acute renal failure (*Nomani et al., 2014*) (Table 17).

**Table 17**. The most important studies reported in literature on mannitol-induced acute renal failure (after *Nomani et al., 2014*)

| Author | Year | Patients with acute renal failure (n=) | Primary diagnosis | CNS insult |
|---|---|---|---|---|
| *Kim et al., 2014* | 2014 | 153 | Intracerebral hemorrhages | Yes |
| *Fang et al., 2010* | 2010 | 53 | Brain trauma | Yes |
| *Chen et al., 2007* | 2007 | 94 | Subarachnoid hemorrhage | Yes |
| *Gondim et al., 2005* | 2005 | 11 | Intracerebral hemorrhages | Yes |
| *Dziedzic et al, 2003* | 2003 | 0 | Intracerebral hemorrhages | Yes |

Used for almost a century in reducing brain edema, mannitol is still used as a standard in IH management, also being recommended in consensus by all guides. Nonetheless, further researches are imperative in order to obtain the optimal mannitol pharmacokinetic model (*Turliuc et al., 2019*).

### I.2.4.2. The use of microporous polysaccharide hemispheres from potato starch in neurosurgery: safety, efficiency and applicability

Regarding the hemostasis in neurosurgery, topical agents represent a real arsenal for neurosurgeons (*Turliuc et al., 2018*). Even though most brain surgeons currently use electrocoagulation and other hemostatic agents for achieving hemostasis, which have become widespread, after the 2000s, a new agent appeared in surgery, i.e. microporous polysaccharide hemispheres (MPHs) (Arista™ AH, TraumaDex™, Bleed-X™, HemaDerm™), which are spherical particles of predetermined porosity, made of polysaccharides of vegetable origin. Through their mechanism (Figure 39), these MPHs have proven their safety and efficiency in achieving topical hemostasis, both in clinical studies (Table 18, Table 19) as well as in models on animals (Table 20).

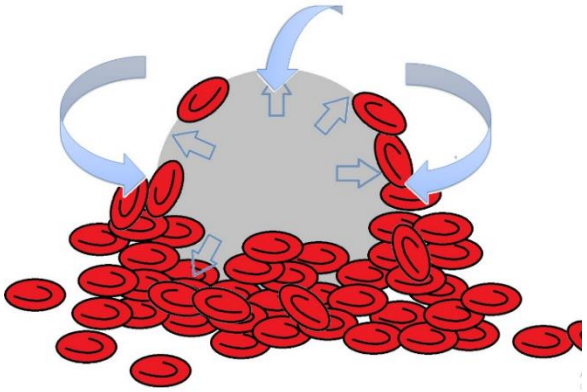

**Figure 39.** Microporous polysaccharide hemispheres mechanism of hemostasis. Hemispheres (gray) act as a molecular sieve that expands by absorbing the fluid and concentrating platelets, erythrocytes and blood proteins on the surface of the particles (from *Turliuc et al., 2018*)

**Table 18**. Clinical studies of microporous polysaccharide hemispheres (from *Turliuc et al., 2018*)

| Author | Medical field | Procedure | Patients (MPHs) | Hemostasis obtained after MPH application | Adverse reactions |
|---|---|---|---|---|---|
| *Reynbakh et al., 2018* | interventional | electrophysiology device implantation | 77 | significant reduction in the rate of overall post-procedural complications, reduction of the infection and implantation site hematoma rate | no |
| *Bruckner et al., 2014* | thoracic surgery | cardiothoracic surgical procedures | 103 | significant reduction in hemostasis | no |
| *Nunez-Nateras et al., 2013* | urology | radical prostatectomy | 10 | the postoperative decrease in hemoglobin was less | - |
| *Antisdel et al., 2009* | ENT | endoscopic sinus surgery | 40 | 40% reduction in bleeding | no |
| *Sindwani et al., 2009* | ENT | endoscopic sinus surgery | 65 | 30-45 seconds | no |
| *Tan and Tope, 2004* | dermatology | Mohs micrographic surgery | 22 | did not have an increased incidence of active bleeding upon dressing removal | no |

**Table 19**. Clinical studies of microporous polysaccharide hemispheres in neurosurgery (from *Turliuc et al., 2018*)

| Author | Neurosurgical procedures | Patients | Hemostasis | Adverse reactions |
|---|---|---|---|---|
| Tschan[34] | Glioma, meningioma, brain metastasis, microsurgical brain tumor resection | 33 | 8-202 seconds (mean 57 seconds) | no |
| Galarza[35] | 5 cerebral convexity meningiomas, 5 corticosubcortical gliomas | 10 | <2 minutes | no |

(*Tschan et al., 2011, Galarza et al., 2011*)

**Table 20**. Experimental studies in microporous polysaccharide hemispheres (from *Turliuc et al., 2018*)

| Author | Medical field | Model | | Hemostasis | Observations |
|---|---|---|---|---|---|
| Ereth[16] | Brain surgery | Rat | 228 | 60 seconds | Equally effective hemostatic properties with other hemostatics, no foreign body reaction |
| Antisdel[8] | Intact sinonasal mucosa | Rabbit | 10 | - | No foreign material or foreign body reaction |
| Humphreys[13] | Laparoscopic trocar injury to the spleen | Porcine | 3 | 165.3-200.7 seconds | - |
| Humphrey[19] | Laparoscopic renal injuries | Porcine | 4 | 100.2-196.2 seconds | No foreign body reaction |
| Ersoy[44] | Severe femoral artery bleeding | Rat | 6 | 30, 60, 90 seconds | MPHs and compression significantly decreased the time of hemostasis |
| Biondo-Simoes[7] | Heaptic injuries | Rat | 10 | 6 minutes | - |
| Murat[20] | Laparoscopic partial nephrectomy | Porcine | 6 | 2 minutes (range of 1-3) | Provides effective parenchymal hemostasis |
| Murat[6] | Open partial nephrectomy | Porcine | 12 | 2.67-4.67 minutes | No complications, no evidence of residual foreign material |

(*Ereth et al., 2008, Antisdel et al., 2008, Humphreys et al., 2008a, Humphreys et al., 2008b, Ersoy et al., 2007, Biondo-Simoes et al., 2007, Murat et al., 2006, Murat et al., 2004*)

Hemorrhage after cerebral tumor surgery is encountered in 0.8%-1.5% out of 50 cases, and in the case of malignant brain tumors, it reaches up to 4% (*Chang et al., 2003, Henke et al., 2006*).

In the surgical treatment of cerebral cancer, the most widely used is bipolar coagulation, namely electric tissue coagulation. Nevertheless, diffuse bleeding could be difficult to achieve with bipolar coagulation, and moreover, this hemostasis technique leads to the widening of the working channel (*Kalfas and Little, 1988, Palmer, 1994*).

Various studies have demonstrated that using MPHs in neurosurgery has several advantages, including: speed and efficiency in achieving hemostasis, especially in superficial brain bleeding, reducing surgical time and use of electric coagulation (*Tschan et al., 2011, Galarza et al., 2011*). Moreover, it can be easily applied on tumor bed, with the help of a plastic device applicator (*Galarza et al., 2011, Gazzeri et al., 2009*).

Regarding the inflammatory reaction of MPHs, Ereth *et al*. observed the same reaction as in most hemostatic agents (*Ereth et al., 2008*). Another advantage worth mentioning of using MPHs in neurosurgery is the fact that they do not interact with arachnoid villi. In this regard, Tschan *et al*. noticed that applying MPHs on the human brain (25% of the cases had cerebral

ventricles opened during surgery) did not lead to the development of postoperative hydrocephalus (*Tschan et al., 2011*).

In order to improve the efficiency of those MPHs, various authors have resorted to experimental studies (Table 21), however, the results they obtained *in vitro* could not be used in human models, mainly due to poor biodegradability and toxicity (*Turliuc et al., 2018*).

**Table 21**. Experimental studies of chemical microporous polysaccharide hemispheres changes (*Turliuc et al., 2018*)

| Author | Chemical modifications of MPHs | Evaluated | Conclusion | Disadvantage |
|---|---|---|---|---|
| Chen[61] | Cationic modified starch microspheres (CS) | Hemostatic performance | Induced the adhesion of red blood cell and platelet (activated the blood chemical coagulation system due to positive charge, improved the degradation of CS | - |
| Chen[21] | Calcium-modified microporous starch | Hemostasis efficiency, degradation behavior | Improved hemostatic performance and degradability | - |
| Björses[32] | N-Octenylsuccinic anhydride, chloroacetic acid, acetic anhydride diethylaminoethyl chloride and ellagic acid | Thrombin generation, platelet adhesion | Superior in haemostatic capacity | Toxic modifications, poor degradability |

(*Chen et al., 2017, Chen et al., 2015, Björses and Holst, 2009*)

# I.3. Researches on brain and spinal cord injuries

## I.3.1. Researches on the effects of drug treatment in brain injuries

### I.3.1.1.Cerebrolysin effect on the functional recovery and clinical outcome after head injuries

***Background***

Traumatic brain injuries (TBIs) are an extremely important medical and public health problem worldwide (*Majdan et al., 2016, Rubiano et al., 2015*). Due to the fact that the incidence of craniocerebral trauma is underestimated and society is unaware of the impact of TBIs, the consequences not being immediately visible, they have been called *silent epidemic* (*Koskinen and Alaranta, 2008*, *Peeters et al., 2015*). Futhermore, TBIs represent a threatening cause of mortality and morbidity among the young population (*Majdan et al., 2016*), and their incidence is increasing in people over the age of 65, especially in high-income countries (*Majdan and Mauritz, 2015, Roozenbeek et al., 2013*).

According to CENTER-TBI, a large European research project aiming to improve the care for pacients with TBIs, in Europe, 2.5 million people are suffering a traumatic brain injury (TBI) annually, 1 million among them being admitted to the hospital and 75.000 dying. Furthermore, TBI represents the main cause of mortality and significant disability in adults (**CENTER-TBI*).

TBIs have devastating consequences in terms of cognitive, social and psychological functioning, and therefore, the management of patients with TBI is important not only for increasing survival, but also for preventing long-term disabilities.

*In the period 2005-2010, our Department of Neurosurgery at Prof. Dr. Nicolae Oblu Iași participated together with other 9 neurosurgery departments from Romania, in a retrospective study which included 7769 patients with head trauma, that monitored the effect of the treatment with Cerebrolysin in 1618 patients. The results of this study have been published in an original article in a journal indexed in ISI Web of Science and the summary of the most important data are presented here, in the followings:*

Muresanu DF, Ciurea AV, Gorgan RM, Gheorghita E, Florian SI, Stan H, Blaga A, Ianovici N, Iencean SM, **Turliuc D**, Davidescu HB, Mihalache C, Brehar FM, Mihaescu AS, Mardare DC, Anghelescu A, Chiparus C, Lapadat M, Pruna V, Mohan D, Costea C, Costea D, Palade C, Bucur N, Figueroa J, Alvarez A. *A retrospective, Multi-Center Cohort Study Evaluating the Severity-Related Effects of Cerebrolysin Treatment on Clinical Outcomes in Traumatic Brain Injury*. CNS&Neurological Disorders - Drug Targets 2015, 14-(5):587-599. (Impact Factor in 2015 = 1.994)

*This article has 11 ISI citations.*

***Materials and methods***

In the period from 2005 to 2010, our Neurosurgery Department from *Prof. Dr. Nicolae Oblu* Iași participated, together with other 9 neurosurgery departments from Romania, in a retrospective

study which included 7769 patients with traumatic brain injury. Among them, 1618 received *Cerebrolysin*® as adjuvant therapy, starting with the first 48 hours after the trauma. The inclusion criteria were represented by: mild to severe closed head injury, age over 18 years old, admission within 48 hours of TBI onset and follow-up at 10 and 30 days (*Muresanu et al., 2015*).

The patients underwent assessment upon admission, using the same strandardized protocol. Age, gender, GCS score, etiology, medical history, clinical neurological examination (Table 22), CT results (Table 23), surgical intervention and concomitant medication were recorded.

**Table 22**. Neurological symptomatology in each study group (from *Muresanu et al., 2015*)

| Symptom-Sign | Control N (%) | Cerebrolysin N (%) | Significance (Chi-Square) |
|---|---|---|---|
| Coma | 760 (12.35) | 467 (28.86) | $X^2$: 262.47; df:1; p<0.001 |
| Intracranial Hypertension | 1,213 (21.34) | 622 (38.44) | $X^2$: 248.90; df:1; p<0.001 |
| Hemiparesis | 470 (7.64) | 311 (19.22) | $X^2$: 189.99; df:1; p<0.001 |
| Headache | 3,642 (59.20) | 567 (35.04) | $X^2$: 301.37; df:1; p<0.001 |
| Memory disturbance | 295 (4.79) | 135 (8.34) | $X^2$: 13.12; df:1; p<0.001 |
| Confusion | 440 (7.15) | 75 (4.63) | $X^2$: 30.84; df:1; p<0.001 |
| Somnolence | 249 (4.08) | 67 (4.14) | $X^2$:0.03; df:1; ns |
| Agitation | 155 (2.51) | 45 (2.78) | $X^2$: 0.35; df:1; ns |
| Aphasia | 192 (3.12) | 35 (2.16) | $X^2$: 4.15; df:1; p< 0.05 |
| Sensory deficit | 77 (1.25) | 29 (1.79) | $X^2$: 2.78; df:1; ns |

Differences between groups for the distribution of the indicated parameters were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

**Table 23**. Head CT scan findings in each study group at admission (from *Muresanu et al., 2015*)

| CT Result | Control N (%) | Cerebrolysin N (%) | Significance (Chi-Square) |
|---|---|---|---|
| Normal | 2,882 (46.85) | 393 (24.28) | $X^2$: 267.49; df:1; p<0.001 |
| Contusion | 1,333 (21.67) | 699 (43.20) | $X^2$: 307.45; df:1; p<0.001 |
| Dilaceration | 222 (3.60) | 171 (10.56) | $X^2$: 129.19; df:1; p<0.001 |
| Extradural hematoma | 330 (5.36) | 151 (9.33) | $X^2$: 34.72; df:1; p<0.001 |
| Subdural hematoma | 887 (14.42) | 288 (17.79) | $X^2$: 11.40; df:1; p<0.01 |
| Subarachnoid hemorrhage | 397 (6.45) | 109 (6.73) | $X^2$: 0.17; df:1; ns |
| Cerebral edema | 528 (8.58) | 170 (10.50) | $X^2$: 5.79; df:1; p<0.05 |
| Fracture | 1,361 (22.12) | 449 (27.75) | $X^2$: 22.67; df:1; p<0.001 |
| Intraparenchymal hematoma | 25 (0.40) | 16 (0.98) | $X^2$: 8.28; df:1; p<0.01 |

CT: Computerized Tomography. Differences between groups for the distribution of the indicated parameters were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

Furthermore, the patients were evaluated based on the Glasgow Outcome Scale (GOS) and Modified Rankin Disability Score (mRDS) 10 and 30 days after TBI (Table 24). The patients who were treated with Cerebrolysin were grouped in 2 different drug regimens (20 or 30 ml/day, administered through i.v., each of the groups being compared with the control group. Among the patients who received Cerebrolysin, 1142 got 20ml/day and 476 got 30 ml/day dose. The median treatment duration was of 10 days, varrying between 1 and 30 days (*Muresanu et al., 2015*).

**Table 24**. Particular GCS scores and GCS score-related severity in each study group (from *Muresanu et al., 2015*).

| GCS Score | Control | Cerebrolysin | Significance |
|---|---|---|---|
| | N (%) | N (%) | |
| 3 | 132 (2.1) | 47 (2.9) | |
| 4 | 177 (2.9) | 97 (6.0) | |
| 5 | 63 (1.0) | 60 (3.7) | |
| 6 | 154 (2.5) | 79 (4.9) | |
| 7 | 123 (2.0) | 96 (5.9) | |
| 8 | 111 (1.8) | 88 (5.4) | |
| 9 | 101 (1.6) | 56 (3.5) | |
| 10 | 137 (2.2) | 98 (6.1) | |
| 11 | 107 (1.7) | 88 (5.4) | |
| 12 | 259 (4.2) | 164 (10.1) | |
| 13 | 250 (4.1) | 157 (9.7) | |
| 14 | 789 (12.8) | 259 (16.0) | |
| 15 | 3,748 (60.9) | 329 (20.3) | |
| **Average GCS Score** | **Mean±SD** | **Mean±SD** | **Significance (t-Test)** |
| | 13.20±3.26 | 10.94±3.76 | F: 200.57; df:7767; p<0.001 |
| **GCS-Related Severity:** | **N (%)** | **N (%)** | **Significance (Chi-Square)** |
| 3-8 (severe)<br>9-12 (moderate)<br>13-15 (mild) | 760 (12.4)<br>604 (9.8)<br>4,787 (77.8) | 467 (28.9)<br>406 (25.1)<br>745 (46.0) | $X^2$: 632.57; df:2; p<0.001 |
| Total number of cases | 6,151 (100) | 1,618 (100) | |

GCS: Glasgow Coma Scale. Differences between groups for the distribution of the indicated parameters (GCS score; GCS-related severity) were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

***Results***

The mean age of patients treated with Cerebrolysin was of 49.4 ± 19.0 years (range 18-95 years) which was significantly higher than that of the control pacients (46.0 ± 19.4). Furthermore, significant differences were also found between the study groups as regards the distribution of TBI etiologies (*Muresanu et al., 2015*). The demographic and etiological characteristics of the TBI study groups can be seen in Table 25.

**Table 25**. Demography and etiological characteristics of the TBI (from *Muresanu et al., 2015*)

| Parameter | | Control | Cerebrolysin | Significance (t-Test; Chi-Square) |
|---|---|---|---|---|
| | | Mean ± SD | Mean ± SD | |
| Age (years) | | 46.0 ± 19.4 | 49.4 ± 19.0 | p< 0.001 |
| | | N (%) | N (%) | |
| Gender Male/Female | | 4.233/1.918 (68.8/32.2) | 1.182/436 (73.0/27.0) | $X^2$: 10.88; df:1; p<0.01 |
| TBI etiology | Car crash | 3.062 (49.8) | 664 (41.0) | $X^2$: 124.23; df: 6; p<0.001 |
| | Other traffic accidents | 110 (1.8) | 83 (5.1) | |
| | Fall from ground level | 1.131 (18.4) | 345 (21.3) | |
| | Fall from a high level | 641 (10.4) | 195 (12.1) | |
| | Aggression | 1.107 (18.0) | 270 (16.7) | |
| | Loss of consciousness | 31 (0.5) | 30 (1.9) | |
| | Unspecified conditions | 69 (1.1) | 31 (1.9) | |
| Total number of cases | | 6.151 (100) | 1.618 (100) | |

Group means were compared by t-test and differences between groups for the distribution of the indicated parameters were analyzed by using the chi-square test.

*Efficiency of treatment with Cerebrolysin in mild brain injury*

Within the mild TBI subgroup, 4787 patients were treated according to standard medical care alone and 745 received additional treatment with Cerebrolysin (615 patients received 20ml/day and 130 patients received 30 ml/day). In our study, we noticed that GOS mean scores have been significantly higher in the case of patients who received Cerebrolysin at 10 days post TBI (20 and 30 ml/day) compared to the control group (*Muresanu et al., 2015*) (Figure 40).

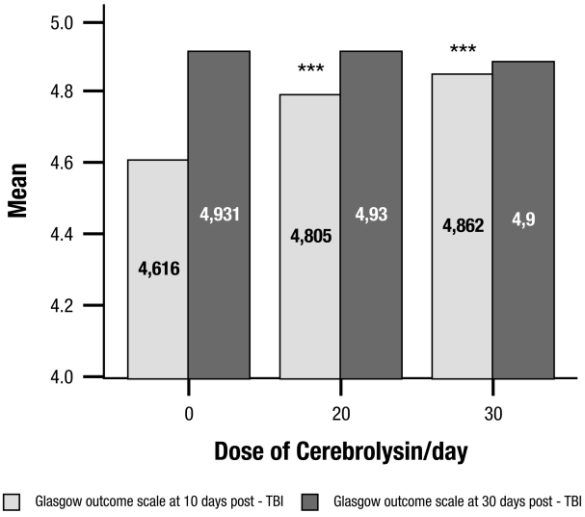


**Figure 40.** "GOS scores at 10 and 30 days post-TBI in the treatment groups of mild TBI patients. The control group is designated as Cerebrolysin 0 ml/day. At 10 days post-TBI, the average GOS score was significantly higher in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. *** = p<0.001 for the Bonferroni post-hoc test at 10 days compared with the controls" (from *Muresanu et al., 2015*)

This means that Cerebrolysin treatment groups had a better outcome, a fact which was also attested by the RDS mean scores (*Muresanu et al., 2015*) (Figure 41).

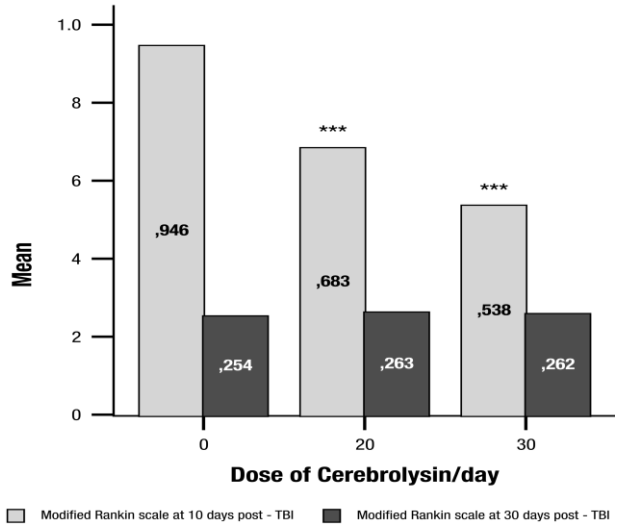


**Figure 41**. "RDS scores at 10 and 30 days post-TBI in the treatment groups of mild TBI patients. The control group is designated as Cerebrolysin 0 ml/day. At 10 days post-TBI, the average RDS score was significantly lower in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. *** = $p<0.001$ for the Bonferroni post-hoc test at 10 days compared with the controls" (from *Muresanu et al., 2015*)

*Efficiency of treatment with Cerebrolysin in moderate TBI*

Regarding the moderate TBI subgroup, 604 patients received standard medical care alone and 406 patients received additional Cerebrolysin (314 patients got 20ml/day and 92 patients got 30 ml/day). Like in the case of the patients with mild TBI who received Cerebrolysin, we noticed that 10 days post TBI, the GOS mean scores was significantly higher both in "20 ml/day and 30 ml/day Cerebrolysin treatment groups ($4.12 \pm 0.99$ and $4.40 \pm 0.81$, respectively) than in the control group ($3.77 \pm 0.98$, $p<0.001$)" (Figure 42). Moreover, the GOS mean scores was significantly higher in the 30 ml/day Cerebrolysin group than in the 20 ml/day Cerebrolysin group ($p<0.05$), meaning a dose-dependent effect (*Muresanu et al., 2015*).

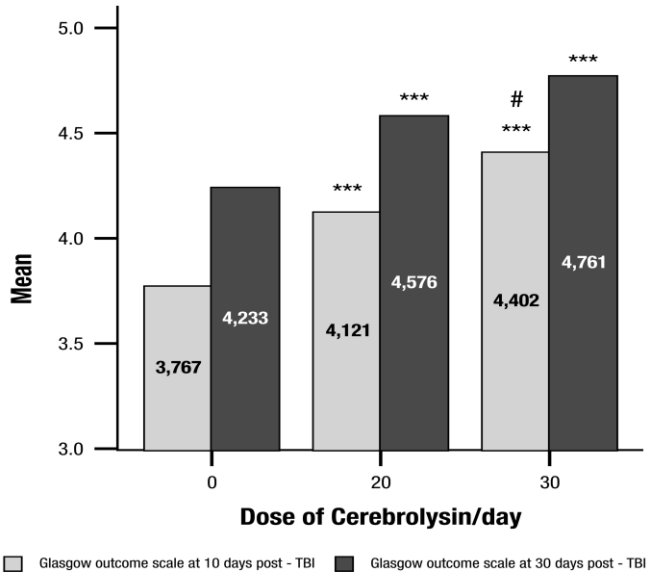

**Figure 42**. "GOS scores at 10 and 30 days post-TBI in the treatment groups of moderate TBI cases. The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average GOS score was significantly higher in both 20 ml and 30 ml Cerebrolysin treatment groups compared to the control group. At 10 days, the average GOS score was significantly higher in the 30 ml Cerebrolysin treatment group compared with the 20 ml Cerebrolysin treatment group. *** = $p<0.001$ for the Bonferroni post-hoc test at 10 and 30 days compared with the controls; # = $p<0.05$ for Cerebrolysin 30 ml/day compared with Cerebrolysin 20 ml/day at 10 days" (from *Muresanu et al., 2015*).

*Efficiency of treatment with Cerebrolysin in severe TBI*

In case of the severe TBI subgroup, 760 patients received standard medical care alone and 467 patients received additional treatment with Cerebrolysin (213 patients got 20 ml/day and 254 patients got 30 ml/day). In the case of these patients, the GOS mean scores was significantly higher both in the 20 ml/day ($2.85 \pm 1.25$, $p < 0.01$) and the 30 ml/day ($3.27 \pm 1.14$, $p<0.001$) in the group of patients who received Cerebrolysin than in the control group ($2.53 \pm 1.32$) 10 days post TBI (Figure 43). Furthermore, the duration of treatment with Cerebrolysin correlated significantly with GOS and RDS scores at 10 days post TBI "(Pearson coefficients of 0.231 and -0.184, respectively, $p<0.001$ for both scores) and 30 days (Pearson coefficients of 0.222 and 0.188, respectively, $p<0.001$ for both scores) post-TBI" (*Muresanu et al., 2015*).

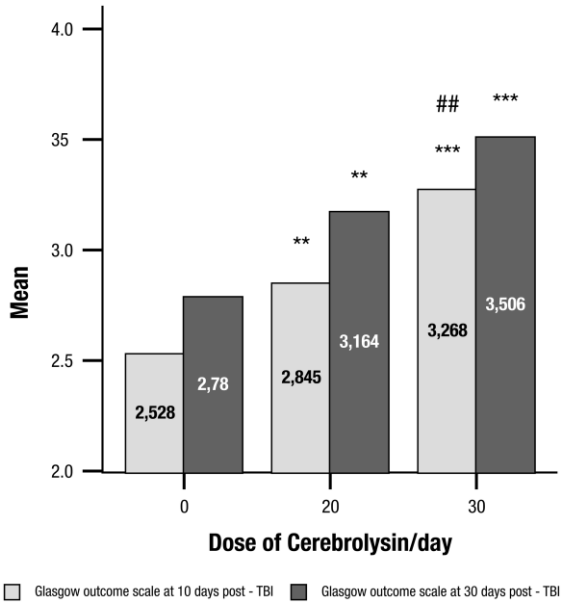


**Figure 43.** "GOS scores at 10 and 30 days post-TBI in the treatment groups of severe TBI patients**.** The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average GOS score was significantly higher in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. At 10 days, the average GOS score was significantly higher in the 30 ml Cerebrolysin treatment group compared with the 20 ml Cerebrolysin treatment group. ** = $p<0.01$ and *** = $p<0.001$ for the Bonferroni post-hoc test at 10 and 30 days compared with the controls; ## = $p < 0.01$ for

Cerebrolysin 30 ml/day compared with Cerebrolysin 20 ml/day at 10 days" (from *Muresanu et al., 2015*)

As regards the safety of Cerebrolysin in head injuries, no treatment-related differences were noticed, with the exception of diarrhea, which was most commonly reported in patients treated with Cerebrolysin ($p<0.01$) (Table 26).

**Table 26**. Adverse events in each treatment group (from *Muresanu et al., 2015*)

| Adverse Event | Control N (%) | Cerebrolysin-20 N (%) | Cerebrolysin-30 N (%) | Significance (Chi-Square) |
|---|---|---|---|---|
| Nausea | 291 (4.73) | 37 (3.23) | 21 (4.41) | $X^2$: 5.00; df:2; ns |
| Diarrhea | 46 (0.74) | 18 (1.57) | 8 (1.68) | $X^2$: 10.34; df:2; p<0.01 |
| Constipation | 682 (11.08) | 105 (9.19) | 41 (8.61) | $X^2$: 5.85; df:2; ns |
| Urinary tract infection | 249 (4.04) | 61 (5.34) | 15 (3.15) | $X^2$: 5.37; df:2; ns |
| Allergic reaction | 21 (0.34) | 3 (0.26) | 1 (0.21) | $X^2$: 0.38; df:2; ns |
| Hypertension | 348 (5.65) | 72 (6.30) | 19 (3.99) | $X^2$: 3.63; df:2; ns |
| Pyrexia | 521 (8.47) | 94 (8.23) | 45 (9.45) | $X^2$: 0.67; df:2; ns |
| Insomnia | 301 (4.89) | 65 (5.69) | 28 (5.88) | $X^2$: 1.97; df:2; ns |

Differences between groups for the distribution of the indicated parameters were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

***Discussions***

The results of our study have demonstrated the efficiency of adding Cerebrolysin at doses of 20 and 30 mg/day to the treatment of TBI, in the sense that we have proved that it improved the clinical recovery of these patients compared with standard medical care alone. Moreover, the treatment with Cerebrolysin has led to the improvement of GOS and RDS measures of clinical outcome, being statistically significant in the subgroup of patients with mild head injury at 10 days post head trauma as well as in the subgroups with moderate and severe brain injury patients both at 10 and 30 days post TBI (*Muresanu et al., 2015*). These results are in agreement with the studies of other authors in the literature who have demonstrated the beneficial effects of Cerebrolysin in head injury (*Alvarez et al., 2013, Alvarez et al., 2008, Alvarez et al., 2003, Chen et al., 2013, König et al., 2006, Onose et al., 2009, Sharma et al., 2010, Wong et al., 2005, Zhang et al., 2013*).

To conclude, the treatment with Cerebrolysin has been demonstrated in this study to be effective and operative in improving functional recovery and clinical outcome after TBIs (*Muresanu et al., 2015*).

### I.3.1.2. Dexamethasone effect in the treatment of chronic subdural hematomas

***Background***

Dexamethasone is a glucocorticoid with a good oral absorption, although it can be administered both intravenously and intramuscularly. It has been used in neurosurgery since 1961 as a treatment for peritumoral brain edema, *Galicich and French* having published an article in this regard (*Galicich and French, 1961*). Currently, dexamethasone is a commonly used medication for the treatment of tumor-related vasogenic edema.

Regarding the treatment of chronic subdural hematomas, most authors have attempted to assess the efficiency of non-operative measures in the management of chronic subdural hematomas through the use of systemic glucocorticoids (*Delgado-López et al., 2009, Soleman et al., 2017, Sun et al., 2005, Thotakura and Marabathina et al., 2015, Zhang et al., 2017*).

*As a result of our collaboration with colleagues from the Department of Neurosurgery at "Sf. Pantelimon" Emergency Hospital, "Dr. Carol Davila" Central Military Emergency University Hospital and the Department of Neurosurgery and Department of Physiology within "Carol Davila" University of Medicine and Pharmacy from Bucharest, Romania, we have published one original research article in a journal indexed in ISI Web of Science and summary of the most important data are presented here, in the followings:*

Papacocea T, Popa E, **Turliuc D**, Papacocea R. *The usefulness of dexamethasone in the treatment of chronic subdural hematomas*. Farmacia 2019, 67(1):140-145. (Impact Factor in 2018 = 1.527)

*This article has 5 ISI citations.*

***Material and methods***

We carried out a retrospective study in the period from 1 January 2016 until 31 December 2017 in the Department of Neurosurgery at *Sf Pantelimon* Emergency Hospital from Bucharest, Romania, on 38 patients diagnosed with chronic subdural hematoma. The inclusion criteria were: patients >18 years old, with grade 1-3 on Modified Rankin Scale and hypodense or isodense subdural hematoma on CT scan. The total number of patients was divided into two subgroups: *group A*, comprised of patients who received dexamethasone and *group B*, with patients who did not receive dexamethasone (*Papacocea et al., 2019*) (Table 27 and 28).

The statistical analysis was performed with SPSS statistical software version 2.0 and we also used the Student test and Chi-square test, the differences being considered statistical significant for $p < 0.05$ (*Papacocea et al., 2019*).

**Table 27**. The demographic characteristics (from *Papacocea et al., 2019*)

| **Parameters** | **Group A (n = 22)** | **Group B (n = 16)** | **p** |
|---|---|---|---|
| Age (years), Mean ± SD | 71.18 ± 8.11 | 72.12 ± 9.38 | 0.74 |
| Gender (f/m)<br>n<br>(%) | <br>15/7<br>68.18/31.81 | <br>11/5<br>68.75/31.25 | <br>0.98 |
| Anticoagulant therapy<br>n<br>(%) | <br>7/22<br>32% | <br>5/16<br>31% | <br>0.94 |

**Table 28**. Dexamethasone treatment protocol (from *Papacocea et al., 2019*)

| Dose | Day |
|---|---|
| 4 mg at 12 hours | 1 - 7 |
| 4 mg once a day | 8 - 14 |
| 4 mg once every two days | 15 - 21 |

***Results and discussions***

We have compared the two subgroups of patients regarding the possibility to avoid surgery in non-emergency cases of patients with cronic subdural hematomas.

In group A of patients treated with dexamethasone, in 59.1% *(n=13)* of the cases, the surgery was avoided, while in group B, only 18.7% (*n=3*) were successfully treated conservatively. This significant statistical difference ($p<0.05$) has clearly demonstrated the benefit of the treatment with dexamethasone when compared to clinical observation alone (*Papacocea et al., 2019*) (Table 29). Moreover, the clinical outcome at 3 weeks using the Modified Rankin Scale are summarized in Table 30.

**Table 29**. The comparasion between the groups regarding the need of surgical intervention (from *Papacocea et al., 2019*)

| Parameters | Group A<br>Dexamethasone treatment (n = 22) | Group B<br>No dexamethasone treatment (n = 16) | p |
|---|---|---|---|
| OPERATED<br>n<br>(%) | <br>9<br>40.9% | <br>13<br>81.3% | 0.0128 |
| NONOPERATED<br>n<br>(%) | <br>13<br>59.1% | <br>3<br>18.7% | |

**Table 30**. The clinical outcome at 3 weeks using the Modified Rankin Scale (from *Papacocea et al., 2019*).

| GROUP A | | | | | GROUP B | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Admission | | 3 weeks | | | Admission | | 3 weeks | |
| mRS Grade | n = 22 | % | n = 22 | % | mRS Grade | n = 16 | % | n = 16 | % |
| **0** | 0 | 0 | 10 | 45.45 | **0** | 0 | 0 | 6 | 37.50 |
| **1** | 4 | 18.18 | 11 | 50.00 | **1** | 3 | 18.75 | 5 | 31.25 |
| **2** | 11 | 50.00 | 1 | 4.54 | **2** | 7 | 43.75 | 2 | 12.50 |
| **3** | 7 | 31.82 | 0 | 0 | **3** | 6 | 37.50 | 2 | 12.50 |
| **4** | 0 | 0 | 0 | 0 | **4** | 0 | 0 | 0 | 0 |
| **5** | 0 | 0 | 0 | 0 | **5** | 0 | 0 | 0 | 0 |
| **6** | 0 | 0 | 0 | 0 | **6** | 0 | 0 | 1 | 6.25 |

Even though there is a long history of using dexamethasone in the treatment of chronic subdural hematomas, it is still controversial nowadays (*Kolias et al., 2018, Miah et al., 2018*). The reason for using glucocorticoids in these types of hematomas is represented by the ability to block inflammatory changes, as well as the blockage of neomembranes formation through inhibiting inflammatory mediators (*Edlmann et al., 2017, Gelabert et al., 2001, Labadie and Glover, 1976, Sun et al., 2005*) and even angiogenesis (*Sun et al., 2005*).

In comparison with similar studies in the literature, the prevention of neurosurgical interventions for patients with chronic subdural hematomas had a rate lower than 59.1%, probably due to the smaller doses used in our study, compared to other studies (*Prud'homme et al., 2016*).

To conclude, conservative treatment with dexamethasone can be effective and safe as a therapeutic option in chronic subdural hematomas, as proven both by the literature and by our study. Dexamethasone can be used with little risk, even in elderly patients with major associated diseases and whose cases surgery would be risky.

Conservative treatment of chronic subdural hematomas involves lower costs, rare serious complications and shorter hospitalization, and this treatment should not be a replacement, but an alternative to surgery in certain cases (*Papacocea et al., 2019*).

### I.3.2. Management of traumatic brain injuries: principles of monitoring and treatment

*Regarding the research carried out on the management of traumatic head injuries in adults, we published two articles indexed in international databases, and summary of the most important data are presented here, in the followings*:

Iordache A, Munteanu R, Coșman M, **Turliuc DM**. *Intracranial pressure monitoring in neurosurgery department in Iași - latest developments.* Romanian Neurosurgery 2012, 19(1).
*This article has 1 citation.*

**Turliuc D**, Cucu A. *Management of mild, and moderate head injuries in adults.* Romanian Neurosurgery 2010, 17(4):421-431.
*This article has 5 citations.*

One of the studies was carried out in the period 2010-2011 in the Department of Neurosurgery at *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iasi and it included 10 patients with GCS<8 points. We have excluded from our study patients with intracranial surgical lesions who underwent surgery. The system used for ICP monitoring was Camino SPM-1 made by Integra, and we used intraventricular catheter – 1104HM type with optic fiber transducer and intraparenchymal catheter-1104B when the cerebral ventricles were reduces in size (*Iordache et al., 2012*) (Figure 44) .

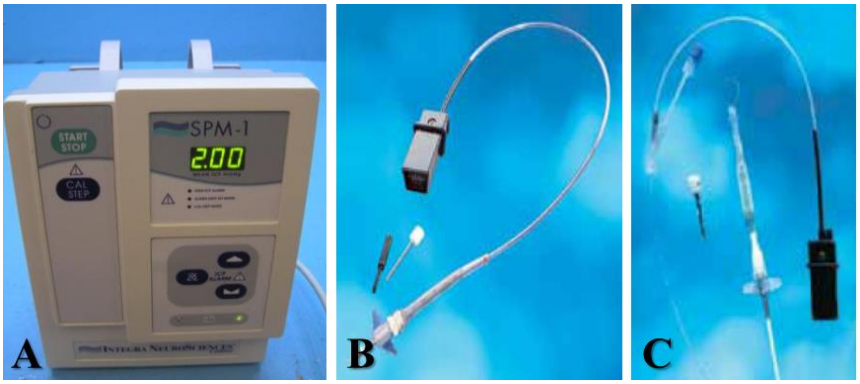


**Figure 44**. Camino SPM-1 system (A) with intraparenchymal catheter (B) and intraventricular catheter (C) (from *Iordache et al., 2012*)

In our study, the head CT scan done on admission has demonstrated different types of lesions, in which cerebral edema predominated in 27% of the cases, and subdural hematoma in 23% of the cases (*Iordache et al., 2012*) (Figure 45).

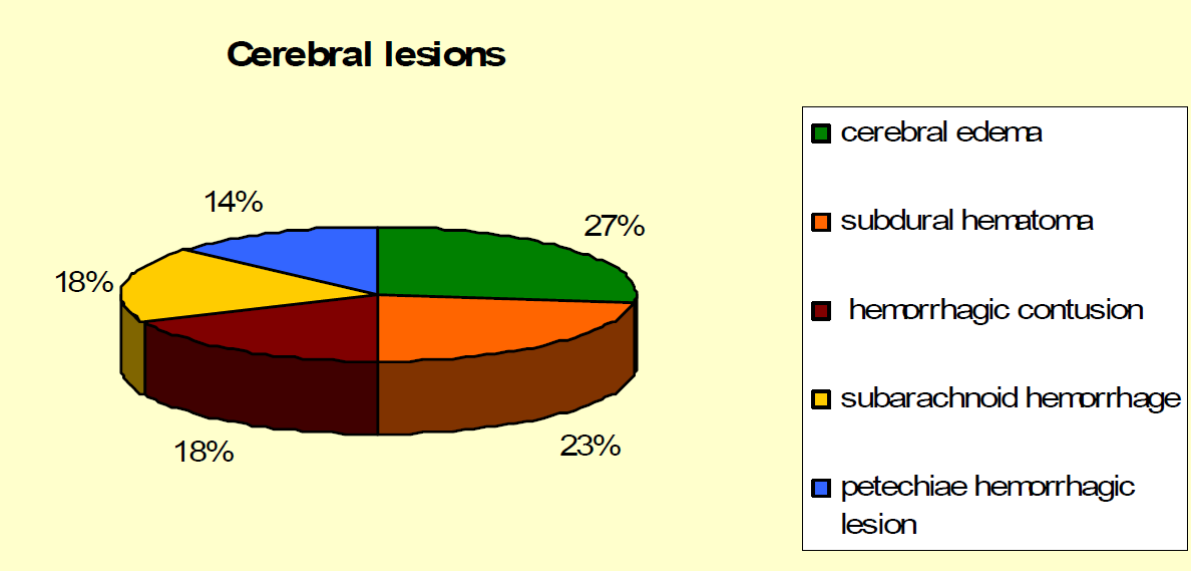


**Figure 45**. Distribution of cerebral lesions found at CT scan (from *Iordache et al., 2012*)

Furthermore, 30% of the patients had cranial base fractures and other 30% temporal bone fractures. As regards neurological status on addmission, the majority of the patients (40%) had GCS 3 (Figure 46), and when it comes to neurological status at discharge, 20% remained with motor deficit and 80% died (*Iordache et al., 2012*).

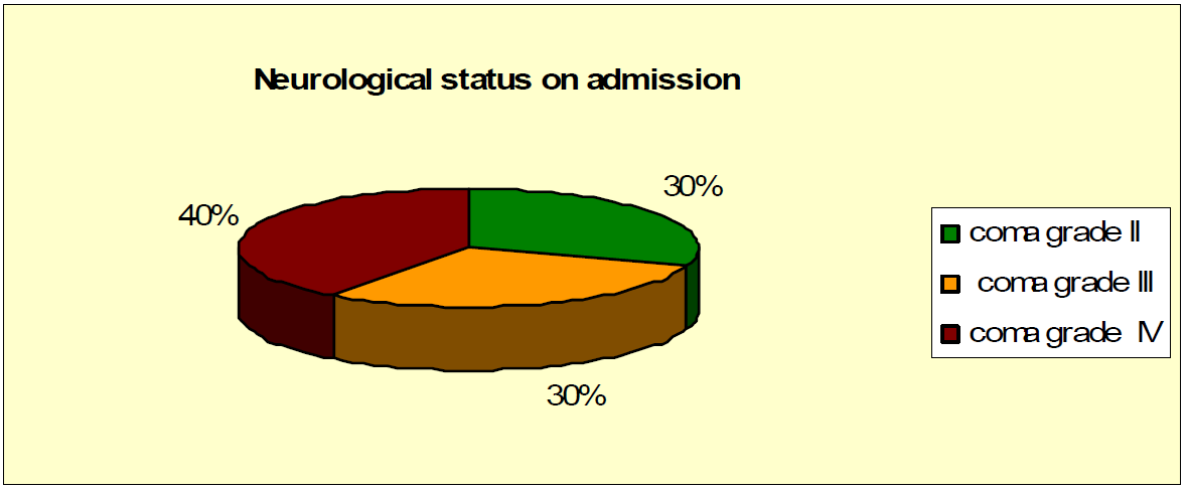


**Figure 46**. Neurological status on admission (from *Iordache et al., 2012*)

To conclude, ICP monitoring is usually safe and the rate of complications when it comes to the technique remains small, even when it is used by inexperienced people. Moreover, in severe cases, ICP monitoring is also useful in supporting the diagnosis of brain death, especially in cases with nonconclusive EEG. Furthermore, our study has shown that it is imperative to reduce the duration

between head injury and therapeutic intervention, namely ICP monitor placement (*Iordache et al., 2012*).

Another study was carried out in the period 2004-2009 in the Department of Neurosurgery at *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital and included 91 patients (66 male and 25 female), aged between 8 and 92 years old. The patients were clinically (GCS) and imagistically assessed through head CT scan upon admission (*Turliuc and Cucu, 2010*).

Out of a total of 91 patients, 35% had minor TBIs (GCS = 14 and 15) and 65% had moderate TBIs (GCS = 9-13). When it comes to their distribution on age groups, we noticed a uniform distribution of the cases, except for those under the age of 9 and over 89, who represented 3% of all patients with head trauma in our study. The length of hospitalization for minor TBIs was 14-15 days and for medium TBIs 15-42 days. As for the etiology of TBIs, most patients (41.7%) were admitted for falling on the same level, followed by car accidents (21.9%) and high level falling (19.7%). At discharge, the great majority of patients were assessed with GOS 2 (44%), followed by those with GOS 3 (29%) and GOS 1 (23%) (*Turliuc and Cucu, 2010*) (Figure 47).

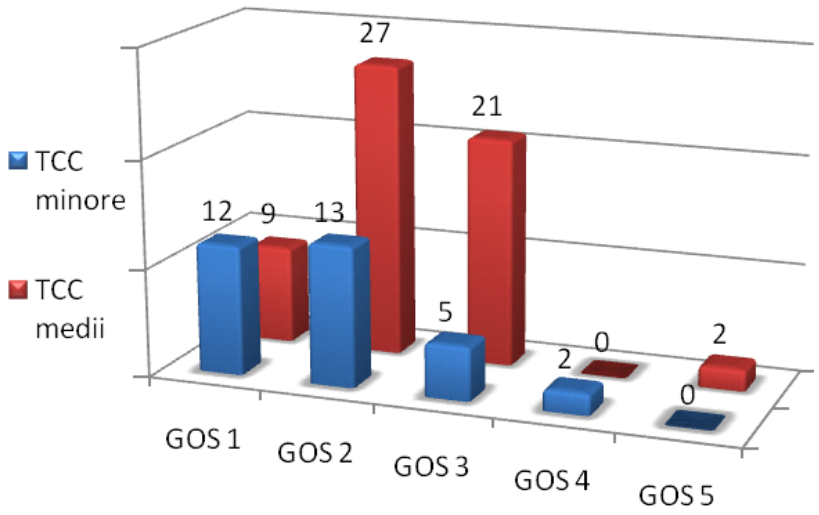


**Figure 47**. GOS distribution according to the type of traumatic brain injury (from *Turliuc and Cucu, 2010*)

To conclude, the evolution of TBIs is influenced by an early diagnosis, by eliminating unnecessary time for diagnosis and by establishing a rapid and appropriate treatment that can be administered by introducing clarifying protocols (*Turliuc and Cucu, 2010*).

### I.3.3. Studies on orbitocranial injuries in children and adults: case studies and literature review

Despite being common in times of war (*Misra et al., 1992, Singh et al., 2003*), cranio-orbital trauma is very rare in the civilians and even though they represent only 0.4% of all TBIs, they have a high mortality (*Kim et al., 2012, Klančnik et al., 2018, Miscusi et al., 2013, Singh et al., 2003*). When a foreign object enters in the intracranial space, transorbital intracranial injuries can lead to severe brain injury, and secondary can also lead to cerebral complications (*Dunya et al., 1995*).

*We have reported two cases of orbital and orbitocranial penetrating injuries, treated in our Department of Neurosurgery at Prof. Dr. Nicolae Oblu Clinical Emergency Hospital of Iași and published in two articles indexed in international databases and summary of the most important data are presented here, in the followings:*

**Turliuc DM**, Cucu AI, Arbore-Sorete R, Dumitrescu GF, Sava A, Costea CF. *Orbitocranial penetrating injury by a metallic foreign body. Case report and anatomical considerations*. Romanian Neurosurgery 2017, 31(4):437-443.

**Turliuc DM**, Costan VV, Cucu AI, Costea CF. *Intraorbital Foreign Body.* Revista Medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi 2015, 119(1):179-184.

*This article has 11 ISI citations and a total of 17 citations.*

The first case is of a 38 year old male patient who was admitted in our Department of Neurosurgery with an orbitocranial penetrating injury (OPI) by a metallic foreign body (work accident). Upon admission, the patient had a GCS=15, with cephalalgia and bradypsychia. The opthalmological examination highlighted a hematoma of the upper right eyelid, an important wound in the upper angle and also no light perception of the right eye (Figure 48). The metallic foreign body was not seen because the patient had extracted it immediately after the accident (*Turliuc et al., 2017*).

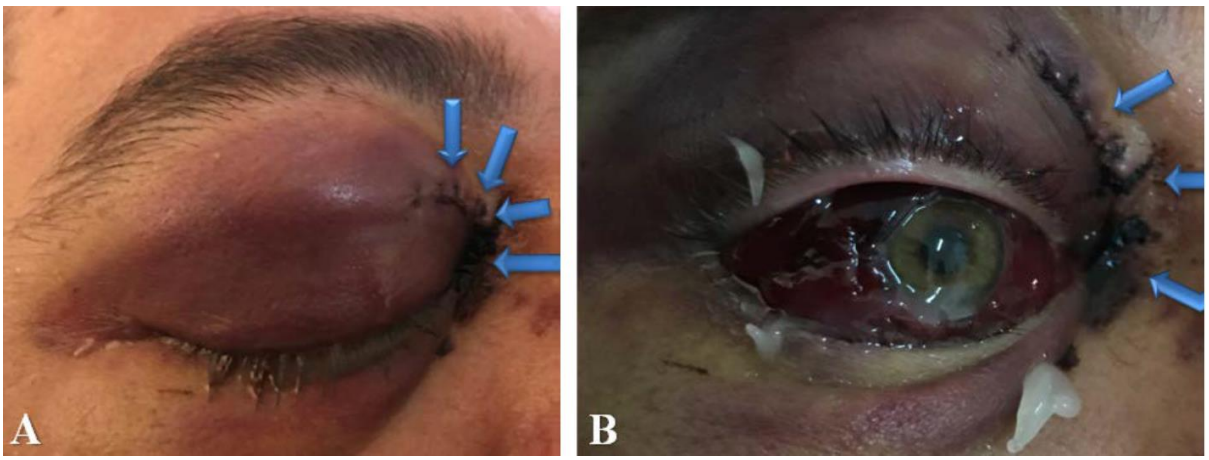


**Figure 48**. Orbital ecchymosis with sutured wound (blue arrows) (A). Right subconjunctival hemorrhage and the entry point of foreign body (blue arrows) (B) (from *Turliuc et al., 2017*)

The head CT scan highlighted an OPI, with an orbital roof fracture and also a intracranial trajectory of the foreign body with right frontal dilaceration and frontal intracerebral hemorrhage (Figure 49). The clinical evolution was favourable, but with loss of vision in right eye (from *Turliuc et al., 2017*).

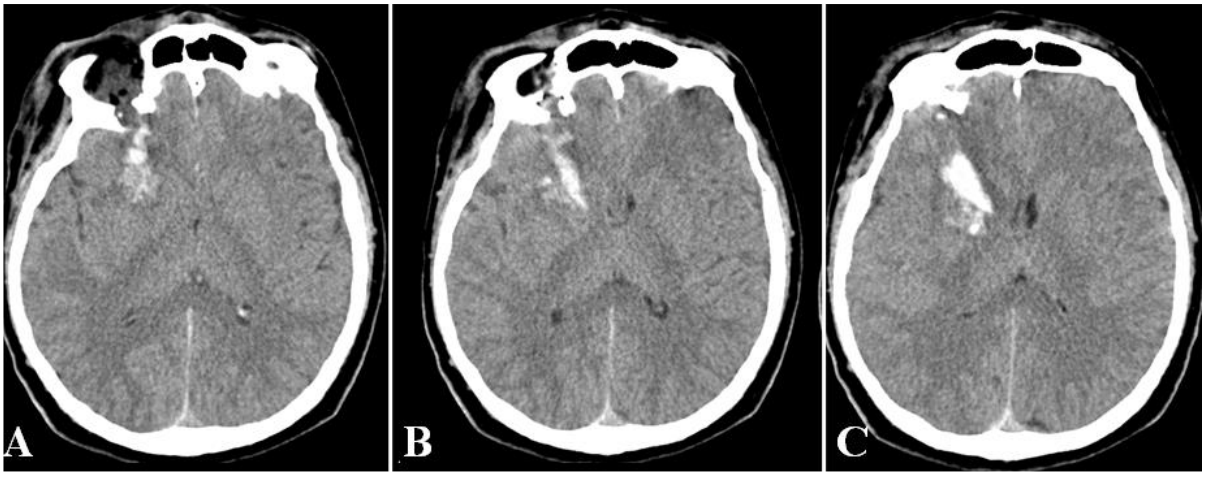


**Figure 49**. "Head CT-scan with: right orbital roof fractures (A, B). right frontal dilaceration and intracerebral hemorrhage (B, C) that respects the trajectory of the foreign body" (from *Turliuc et al., 2017*)

The orbit (Figure 50) is an bone structure shaped like a horizontal pyramid and has two crucial anatomical characteristics which make it vulnerable to orbitocranial penetrating injuries (OPIs): the pyramid shape makes penetrating objects go directly to the orbital apex and from there to the temporal cranial fossa (Figure 50) (*Smely and Orszagh, 1999*) and its thin bony walls make the orbit the most vulnerable anatomical structure at the level of the cranium (*Arslan et al., 2012*, *Turliuc et al., 2017*).

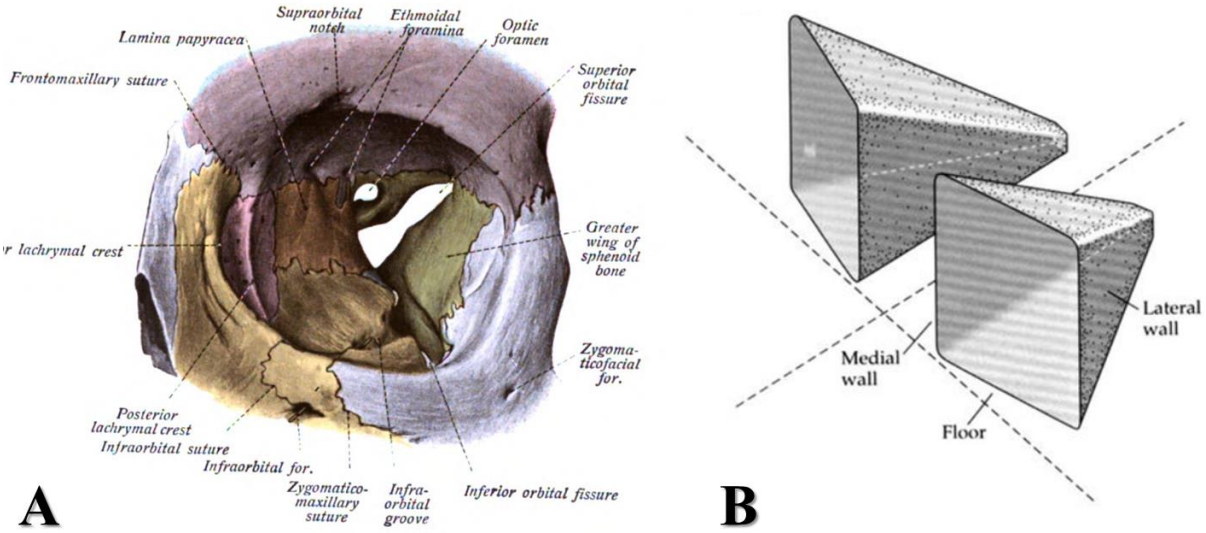


**Figure 50**. The left orbit (anterior view) (A) (from *Sobotta, 1909*). Geometry of the orbits (B). (public domain)

Depending on kinetic energy, OPIs are divided into (1) *injuries with low-velocity* and (2) *injuries with higher-velocity* (*Mackerle and Gal, 2009, Mzimbiri et al., 2016*). In our patient's case, OPI had high-velocity, and this type of trauma produces fractures of the orbital walls and penetrates the intracranial space in a direction of foreign body trajectory (*Lee et al., 1999, O'Neill et al., 1994, Scarfo et al., 1990*). In this case, the foreign body was upward directed and perforated the roof of the orbit, entering the cranial cavity and injuring the frontal lobe (Figure 51).

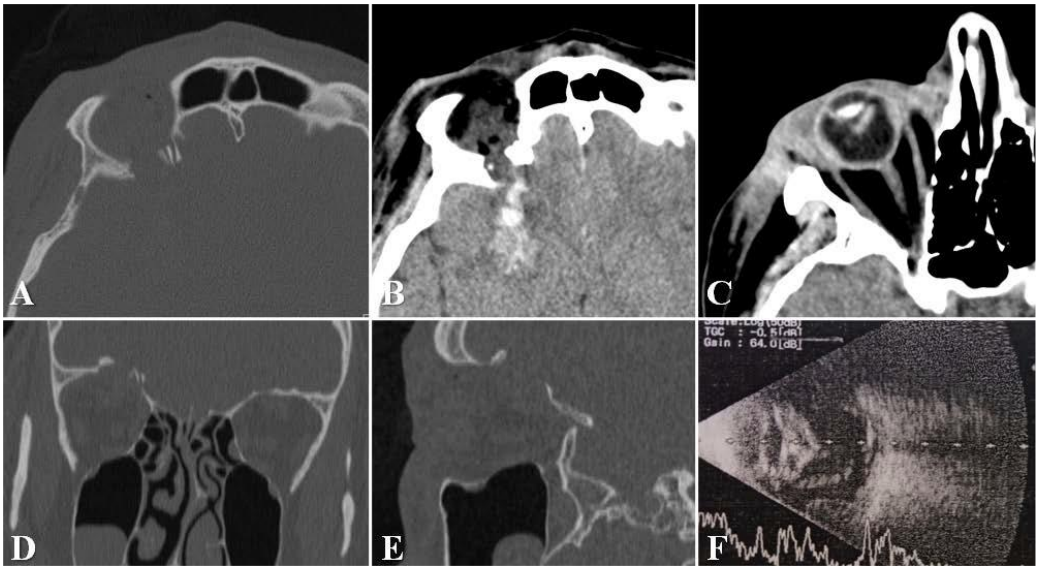


**Figure 51**. "Fracture in the right orbital roof (A, B, D, E). Vitreous hemorrhage and choroidal hematoma (right eyeball)" (C). Retinal detachment with vitreous hemorrhage and choroidal hematoma (ocular ultrasound) (F) (from *Turliuc et al., 2017*)

Of all OPIs with higher-velocity, the most common are those in which the superior wall of the orbit is perforated, and this type of injuries are encountered especially when the patient falls into foreign objects which have an upward direction (*Mzimbiri et al., 2016*). Moreover, this also occurs because people have an instinctive tendency to extend their neck backwards in order to protect themselves from the foreign body (*Mzimbiri et al, 2016, Scarfo et al, 1990*). In this case, the foreign body penetrated the pyramid orbit at the level of the medial canthus (Figure 52) and had a median, postero-superior trajectory through the upper orbital wall towards the intracranial space, producing frontal dilaceration and intracerebral hemorrhage (*Turliuc et al., 2017*).

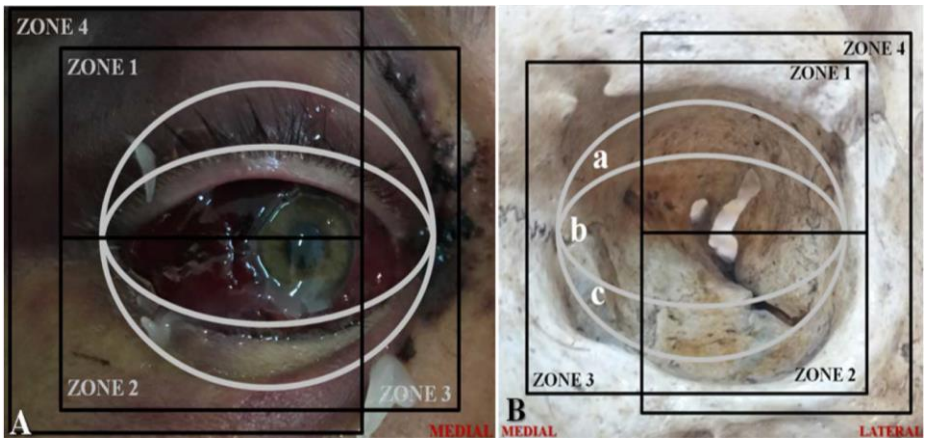


**Figure 52**. "Turbin's diagram of ocular surface applied to our patient (A). Schematic diagram of ocular surface, adapted after *Turbin et al., 2006* (B)". (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*) (from *Turliuc et al., 2017*)

To conclude, a good understanding and knowledge of the clinical neuroanatomy of the orbit and of the different patterns of the orbitocranial trauma are extremely important in order to establish

an early diagnosis as well as an adequate treatment strategy. Moreover, orbital injuries which involve foreign bodies must raise the suspicion of intracranial injury, even in the presence of a minimal neurological or ocular simptomatology, given the fact that a delay in identifying intracranial complications leads to increased morbidity and mortality (*Turliuc et al., 2017*).

The second case of OPI is of a 12 year old boy who suffered from a craniofacial trauma due to an accidental fall while he was playing with another child. During the impact with the ground, he hit a stake set firmly into the ground, a 6 cm long and 1.5 wide wooden fragment (Figure 58). The foreign object penetrated the right orbit through its lower side, directly towards the orbital apex (Figure 53, 54 and 55).

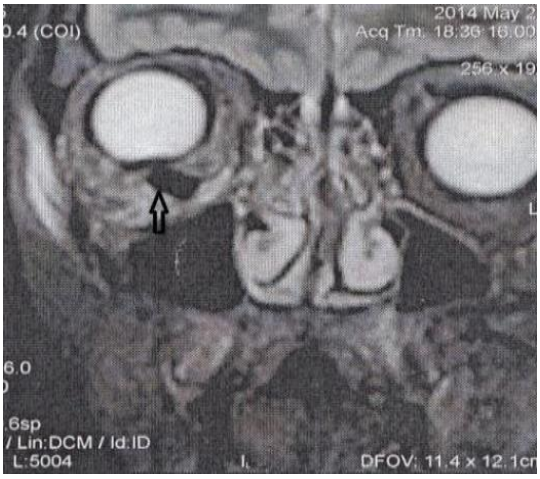


**Figure 53.** Coronal T1WI MRI showing the intraorbital foreign body (black arrow) (from *Turliuc et al., 2015a*)

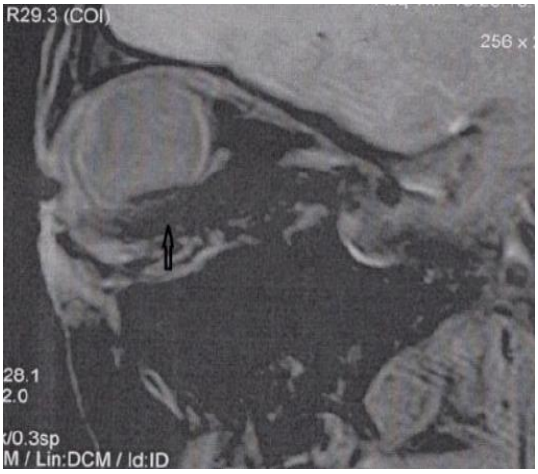


**Figure 54**. Sagittal T1WI MRI showing the intraorbital foreign body (black arrow) (from *Turliuc et al., 2015a*)

The local exam highlighted the external part of the foreign body, immediately under the lower rim of the right orbit, as well as a painful right eye and with important erytema and palpebral edema (Figure 55 and 56).

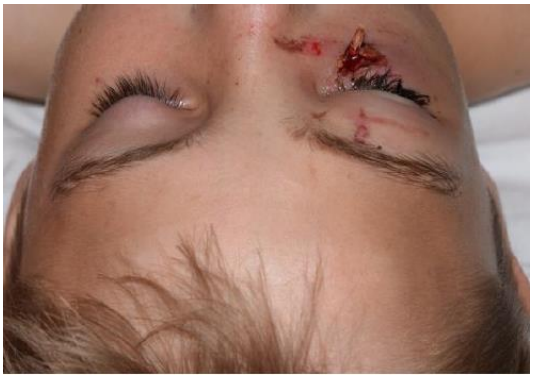

**Figure 55**. Photography of the patient at the first examination: a wooden foreign body, below the right lower orbital rim (from *Turliuc et al., 2015a*)

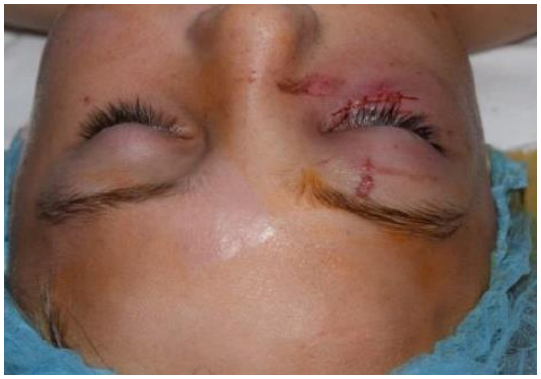

**Figure 56**. Postoperative results (from *Turliuc et al., 2015a*)

At the ophthalmologic examination we noticed that visual acuity was maintained in both eyes. The head CT scan highlighted a right intraorbital hypodensity with a trajectory parallel to the inferior wall of the right orbit. This was completed by a head MRI which showed an intraorbital foreign body, without damaging the intraorbital nerve and vessels (Figure 53, 54 and 57). The surgical treatment consisted in the removal of the wooden fragment by enlarging the entry point (Figure 56 and 58), with a favorable postoperative evolution (*Turliuc et al., 2015a*).

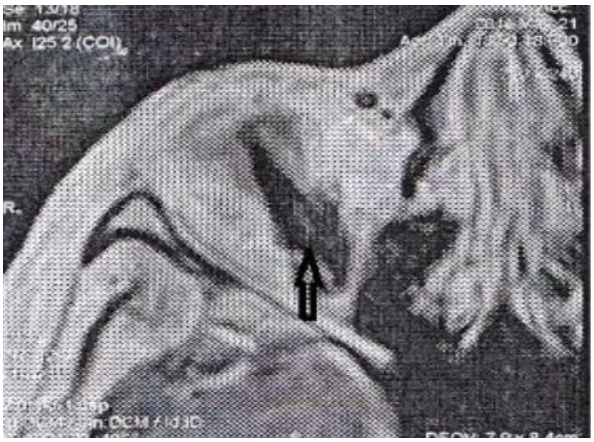

**Figure 57**. Axial T1WI MRI showing the intraorbital foreign body (black arrow) (from *Turliuc et al., 2015a*)

**Figure 58**. Wooden foreign body extracted from the orbit (from *Turliuc et al., 2015a*)

The foreign bodies localized in the anterior 2/3 of the orbit can be approached extracranially, while the foreign bodies localized in the orbital apex, especially in the medial region of the optic nerve, require a transcranial approach. The presence of the periorbita allows the classification of orbital injuries into *intradural* and *extradural* (deep in the periorbita, located between the periorbita and bony walls of the orbit, respectively). Moreover, the muscular cone divides the orbit into *intraconal* and *extraconal* areas (Figure 59). These details are extremely important in the choice of surgical approaches in orbital and OPIs (*Turliuc et al., 2015a*).

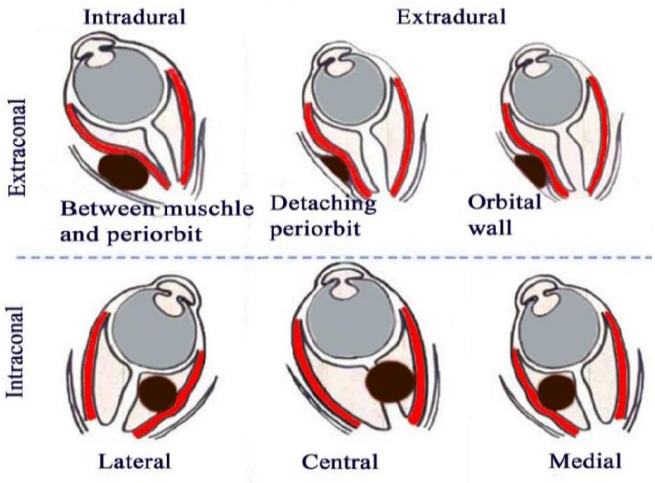


**Figure 59.** Topographic classification of intraorbital lesions (from *Turliuc et al., 2015a*)

To conclude, we have presented this case as peculiar due to the fact that a large foreign body (Figure 58) crossed the entire length of the orbit right to the apex, without causing damage to any intraorbital structures.

The intraorbital foreign body is a surgical emergency and we recommend CT scan as the first method of diagnosis, followed by MRI of the orbit. Furthermore, early surgical diagnosis and treatment influences the evolution and prognosis of the patient's visual acuity (*Turliuc et al., 2015a*).

### I.3.4. Researches on the cervical spinal cord injuries

#### I.3.4.1. Cervical spinal cord gunshot injury: case study and literature review

***Background***

Nowadays, the incidence of spinal cord gunshot injuries has increased and has become an important an worrying cause of mortality and morbidity due to the rising level of violence in urban areas in the young population (*Cook et al., 1999*). Consequently, this incidence of spinal cord gunshot injuries ranges, depending on country, between 13 and 44% (*Farmer et al., 1998, Sidhu et al., 2013*). The patients are aged between 15 and 34 (*Yoshida et al., 1995*) and spinal cord transection with complete deficit occurs in most cases (*de Barros et al., 2002*). Among these, cervical spinal cord gunshot wounds cause most frequently a complete neurological deficit and have a poor prognosis (*Bishop et al., 1991, de Barros et al., 2002, Kupcha et al., 1990*).

We are presenting a rare case of a cervical gunshot wound with a shotgun fire pellets in a woman, the peculiarity of this report consisting in the fact that the gunshot has led to the destruction of the cervical spinal cord, even though cervical spinal cord gunshot injuries with shotgun fire pellets are not currently deadly in people (*Turliuc et al., 2015b*).

**Turliuc D**, Turliuc S, Mihailov I, Cucu A, Dumitrescu G, Costea C. *Homicide by cervical spinal cord gunshot injury with shotgun fire pellets: case report*. International Journal of Medical Research & Health Sciences 2015, 4(4):928-931.

The patient, aged 48, was admitted to the Emergency Department at *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași with a cervical spinal cord gunshot injury and complete neurological deficit. Further investigations showed that she had been shot by her husband, a hunter by profession, during a family dispute, with a shotgun fire pellets in the right supraclavicular region (*Turliuc et al., 2015b*) (Figure 60).

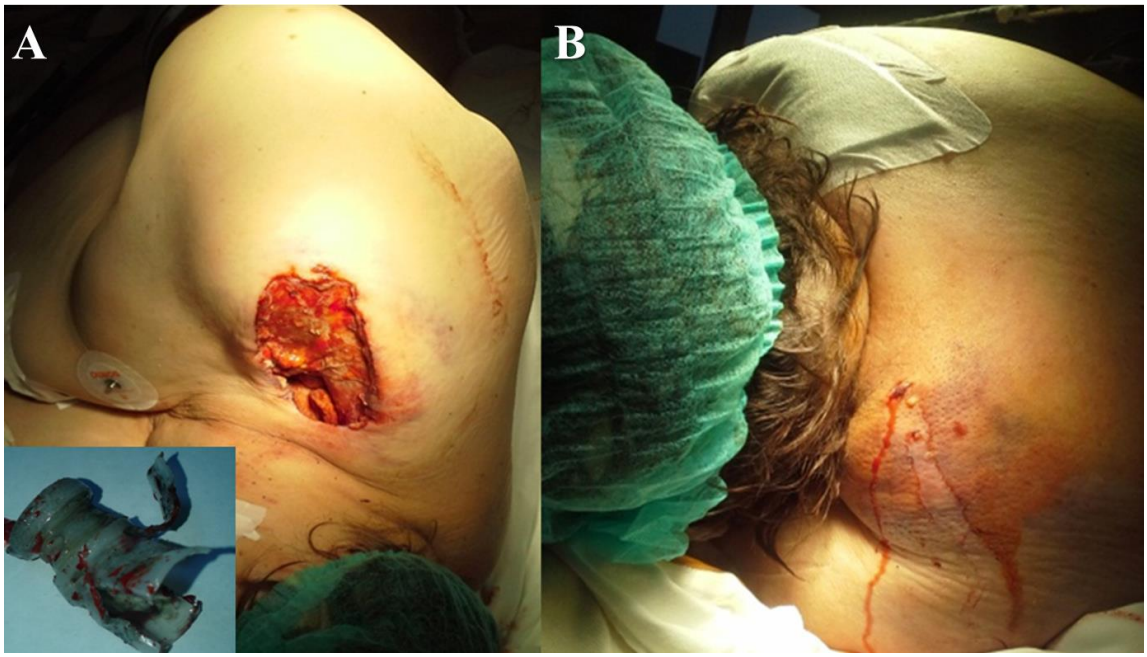


**Figure 60**. Entry wound with plastic wadding of cartridge within (box) (A). The exit wounds of pellets (B) (from *Turliuc et al., 2015b*)

The exit wound was represented by two contusion wounds, smaller than 1 cm, at the level of the left scapular region (Figure 60). Cervical spine CT scan highlighted a cervical spinal cord injury with several foreign bodies (Figure 61). Surgical treatment consisted in primary wound toilet, surgical debridement and extraction of blocked plastic wadding of cartridge and visible pellets (Figure 62), closure of dural leak and defect covering with fasciocutaneous advancement flaps (*Turliuc et al., 2015b*) (Figure 63).

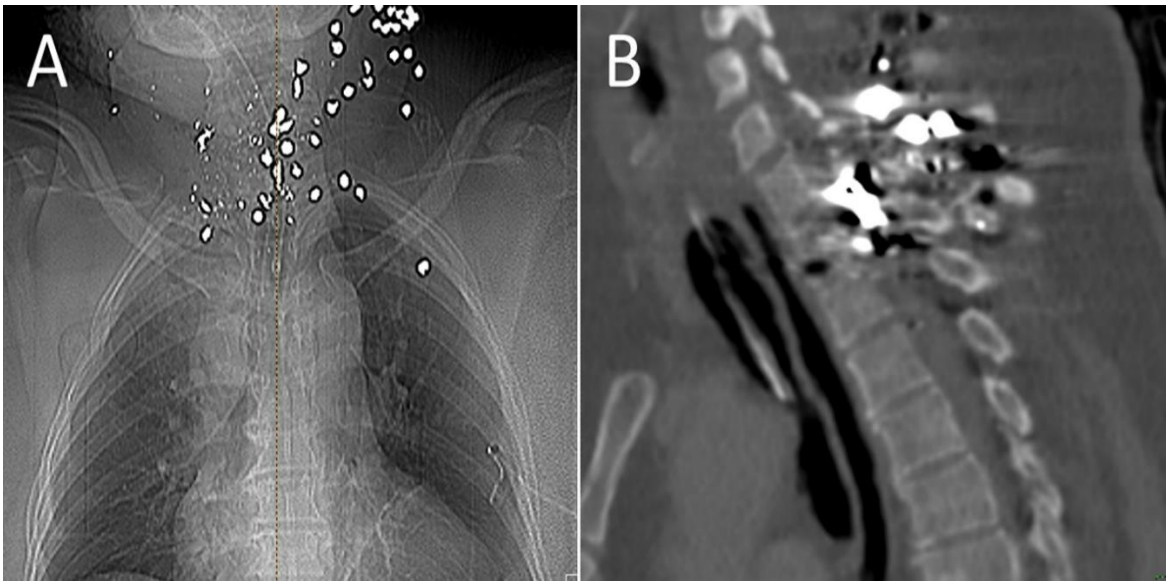


**Figure 61**. CT scan images: foreign metal bodies (A). Pellets in spinal canal in the cervicothoracic junction (B) (from *Turliuc et al., 2015b*)

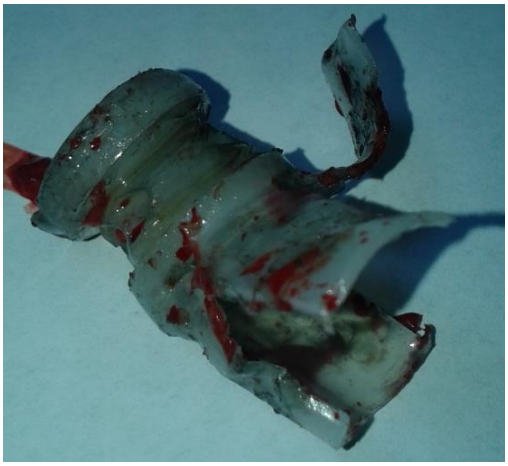

**Figure 62**. Plastic wadding of cartridge (from *Turliuc et al., 2015b*)

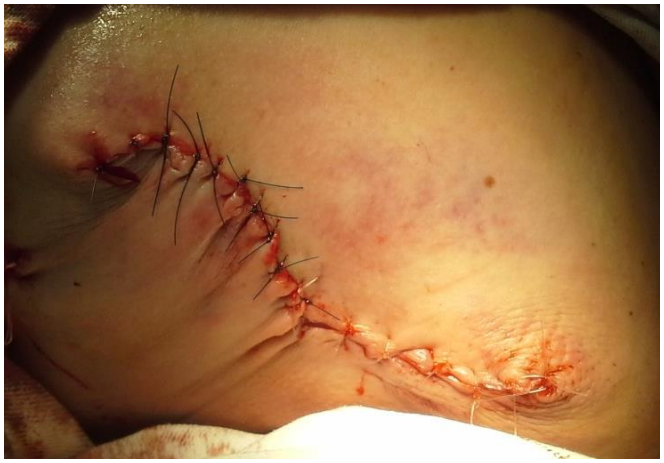

**Figure 63**. Postoperative image: local fasciocutaneous advancement flaps for defect covering (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

In our case, the entrance wound was made by the shotgun cartridge because her husband had put the shotgun in the supraclavicular region. The cartridge then exploded in the right supraclavicular region and created a field of dispersion of pellets throught the right laterocervical region (Figure 64), at the level of the junction of the cervico-thoracic spine, with the exit of pellets through two holes in the left scapular area (Figure 60).

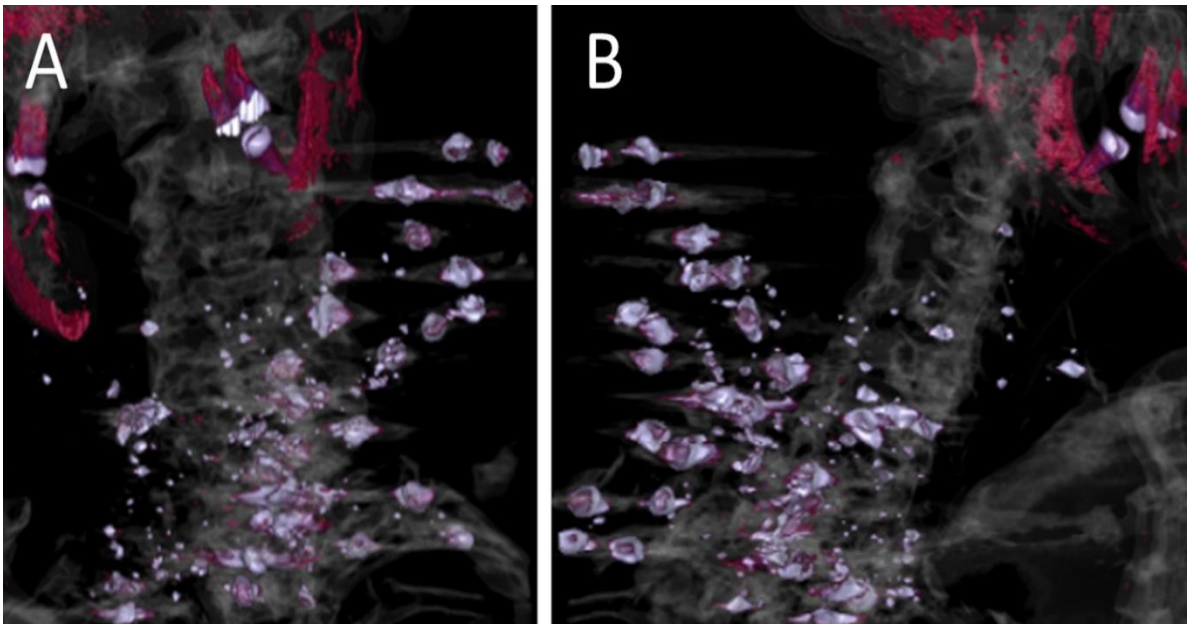


**Figure 64**. "3D reconstruction of pellets distribution: anterior view of cervical spine showing right-left trajectory (A). Right oblique posterior view showing posterior pellets distribution (B)" (from *Turliuc et al., 2015b*)

The pellets (approximatively 40) remained arrested in the soft tissues of laterocervical area and in the spinal canal (C6-T3) (*Turliuc et al., 2015b*) (Figure 65 and 66).

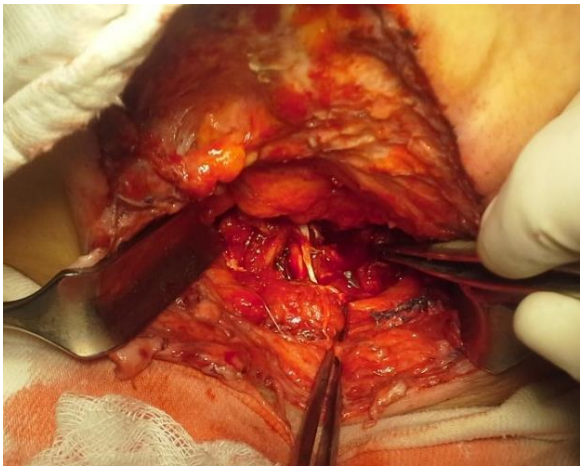

**Figure 65**. Intraoperative image: the hole entry wound produced by shotgun fire cartridge (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

**Figure 66**. Foreign metal body (pellet) (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

Normally, shotgun fire pellets do not produce death injuries, but in this case, the injury was fatal, due to the fact that the gunshot distance was smaller than 0.5 m from the victim, producing an important spinal cord lesion which led to death in the 7$^{th}$ day.

To conclude, the treatment of patients with spinal cord gunshot injuries represents an urgency and requires an multidisciplinary team. In the case with complete neurological deficit, the surgical treatment is not indicated in the great majority of cases, due to the fact that there are no therapeutic resources. It can, however, be taken into account in cases of dural leak, like in our case, installation of toxicity- poisoning (lead bullets), migration of an intracanal cartridge or pellets, progression of neurological deficit or occurrence of spine instability (*Kumar et al., 2011, Waters and Hu, 1991, Turliuc et al., 2015b*).

### I.3.4.2. Research on the occurrence of priapism in spinal cord injury compression

***Background***

Priapism secondary to spinal cord injury is a rare entity and occurs due to the release of neurotransmitters from the parasympathetic nerves who induce erection or interfere with discharge from the sympathetic nervous system (*Gordon et al., 2005, Lue, 2002*). This is encountered in acute complete and cervical spinal cord lesions (*Koyuncu et al., 2019*) and, however, the timming and frequency in spinal cord injuries are still debated (*Todd, 2011*).

Initially encountered in sexually transmitted disease in acient times, priapism was later noticed in spinal cord injuries, the underlying mechanism involved in this pathology becoming known towards of the 18th century, mainly on the strength of neurological observations.

*In a review carried out together with our colleagues from our department and university, we sought all the articles written on priapism in men after acute spinal cord trauma from antiquity to the beginning of the 20th century. This study aims to present a short overview of the clinical observations*

*of traumatic male priapism until the beginning of the 20th century. The results of this study have been published in a review in a journal indexed in ISI Web of Science and the summary of the most important data are presented here, in the followings:*

**Turliuc MD**, Turliuc S, Cucu AI, Tamas C, Carauleanu A, Buzduga C, Sava A, Dumitrescu GF, Costea CF. *Through clinical observation: the history of priapism after spinal cord injuries*. World Neurosurgery 2018, 109:365-371. (Impact Factor in 2018 = 1.723)

The first proof of the existence of priapism is from the Paleolithic period (*Angulo and García-Díez, 2009, Barandiarán et al., 1999, Vialou, 1991, Turliuc et al., 2018a*), and the oldest reference dates back to the 17th century BC in Edwin Smith Surgical Papyrus (Figure 67 and 68) (*Wilkins, 1992*, *Turliuc et al., 2018a*), which describes a case of a cervical fracture with priapism, also with urinary incontinence, seminal emission and quadriplegia: *"if you examinest a man having a dislocation in a vertebra of his neck, shouldst thou find him unconscious of his two arms (and) his legs on account of it, while his phallus is erected on account of it, (and) urine drops from his member without his knowing it; his flesh has received wind; it is a dislocation of a vertebra of his neck extending to his backbone which causes him to be unconscious of his two arms (and) his two legs. If, however, the middle vertebra of his neck is dislocated, it is an emissio seminis which befalls his phallus"* (*Wilkins, 1992, Turliuc et al., 2018a*).

**Figure 67**. Portrait of Edwin Smith (1822-1906), *painted in 1847 by F. Anelli, US National Library of Medicine*. (public domain)

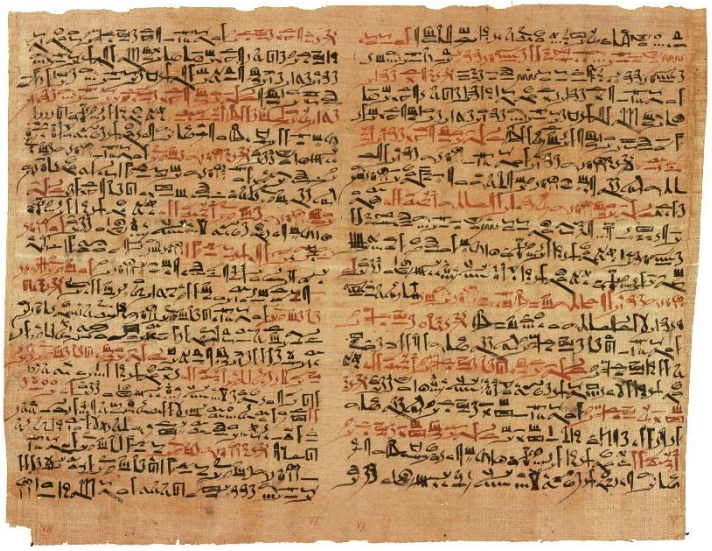

**Figure 68**. Plates VI and VII of the Edwin Smith Papyrus, *The Rare Book Room, New York Academy of Medicine.* (public domain)

Hippocrates believed that the spinal cord was closely linked to the genital organs of the man by a special duct, and the sperm was produced within the spinal cord (*Abbot, 2001, Hippocrates, 1982, Prioreschi, 1996, Turliuc et al., 2018a*). He also considers that a spinal cord trauma produced not only motor deficit but also autonomous disorders of the type of urinary disorders or constipation (*Lifshutz and Colohan, 2004*, *Turliuc et al., 2018a*). The term *priapism* was later introduced by

Claudius Galen (Figure 69), inspired by the name of the god Priapus (*Turliuc et al., 2018a*).

In his treaty *On the Affected Parts*, Galenus not only described priapism, but also attempted to find a cure: *"...priapism is an increase in length as well as circumference of entire male organ without desire for sexual intercourse, and without some acquired heat which some people experience in the recumbent position. Some have outlined the condition as follows....a persistent, unchanging increase in size of the male organ or persistent swelling. It obviously has a name derived from Priapus. For human beings sculpt as well as pain Priapus as one who by nature has such an organ. And to treat priapism, apply the things that were discovered by experience to be naturally efficacious, namely give him [the patient suffering from priapism] yellow waterlily [nymphaia] to drink, the seed of the chastee tree and pale rue mixed with his food"* (*Foucault, 1988, Riddle, 2010, Turliuc et al., 2018a*).

Moreover, Galenus came up with two theories to explain the mechanisms of this pathology, namely: "*the dilated orifices of the arteries* and *the formation of the pneuma in the nerve"* (*Foucault, 1988*, *Turliuc et al., 2018a*).

Later on, Paul of Aegina (625-690) was the first to make the difference between priapism and satyriasis (Figure 70). Furthermore, he also noticed the association between spinal cord injury and priapism and recognized this risk of the spinal cord compression (*Turliuc et al., 2018a*).

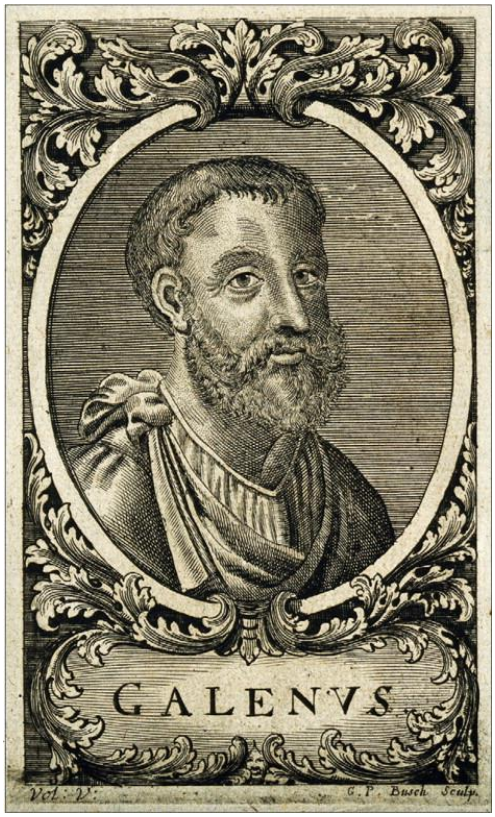


**Figure 69**. Claudius Galenus (129-c.200/2016). (public domain)

**Figure 70**. Nymphs and Satyr, *William Adolphe Bouguereau (1873)*, *Sterling & Francine Clark Art Institute Williamstown* (from *Turliuc et al., 2018a*). (public domain)

Contributions in the field of the physiopathology of spinal cord injuries were also made by Leoardo da Vinci (1452-1519) (Figure 71) and Ambroise Paré (c.1510-1590) who mentioned spinal cord injuries in his work *The Books of Surgery* and even had a few recommendations regarding their treatment (*Jardin and Paré, 2005*).

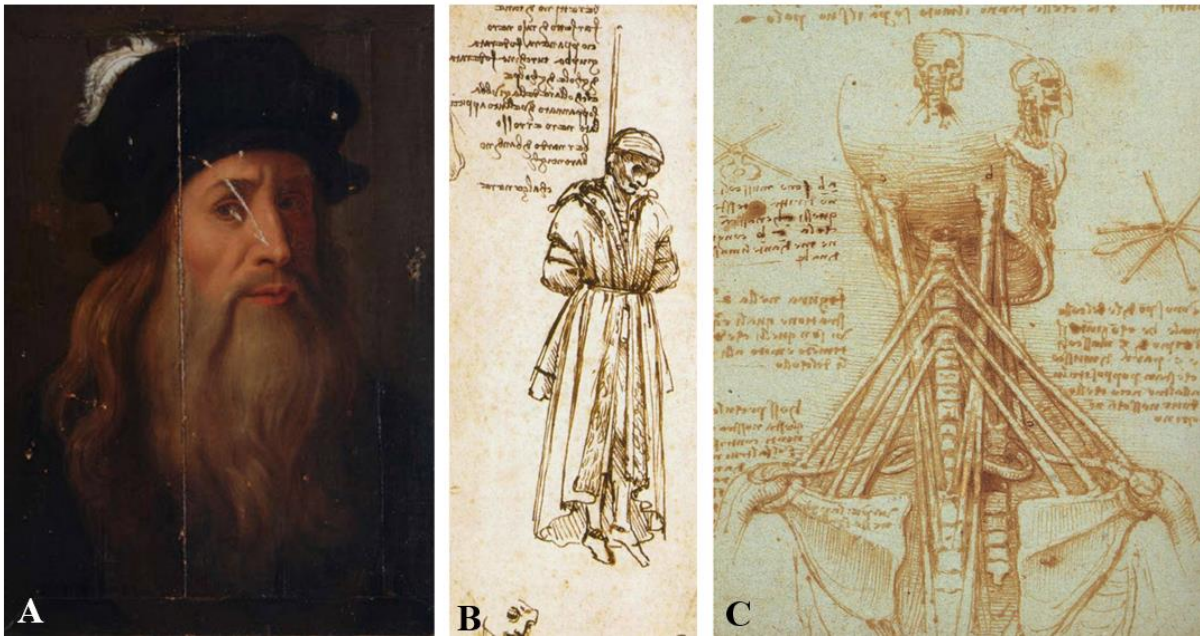


**Figure 71**. Leonardo da Vinci (c.1505), *Museum of the Ancient People of Lucania, Italy* (A). Hanging of the Bernardo di Bandino Baroncelli, *Leonardo da Vinci (1479)*, to which Leonardo attended and observed the appearance of priapism; later he assisted at the postmortem examination (*Turliuc et al., 2018a*) (B). Drawings of Leonardo da Vinci showing the cervical spinal cord (C). (public domain)

Clinical observations about priapism in the context of spinal cord injury and questions on the the physiopathological mechanisms of its occurence continued in the 18$^{th}$ and 19$^{th}$ centuries, when doctors from the most influential European cities started looking for explanations of the mechanisms (*Turliuc et al., 2018a*). These were helped by the knowledge of neurophysiology and neuroanatomy that had begun to shape the division of neurology in European medical schools and hospital settlements (*Smith, 2010*).

In 1847, French surgeon, anatomist and pathologyst Baron Guillaume Dupuytren (1777-1853) reported a cervical fracture with possttraumatic priapism (*Dupuytren, 1847*). Later, in his work *On the injuries and diseases of bone*, he published few cases with cervical spine fractures (*Dupuytren, 1847, Turliuc et al., 2018a*).

Furthermore, the American physiologist Robley Dunglison (1798-1869) mentioned that priapism occurs mainly in trauma of the upper spinal cord rather than the inferior portion of the medulla. Also, he noticed that in most cases, there is an early symptom which appears in the first 2-3 days after trauma (*Dunglison, 1838*). The English surgeon Benjamin Collins Brodie (1783-1862) agreed Dunglison theory on priapism after spinal cord injuries, noting that *"priapism occurs even where the sensibility is entirely destroyed, and may be induced by the mechanical irritation caused by the introduction of the catheter, where the patient is entirely unconscious of the operation"* (*Hall,*

*1841, Turliuc et al., 2018a*).

The 18th century brought the comprehension of the neurophysiological mechanisms of the priapism in context of spinal cord trauma, especially by Albrecht von Haller (1708-1777). Haller was the first to specify the potential neuronal mechanisms in the occurence of erection and priapism, hypothesizing that erection occurs as a result of increased blood supply due to stimulation of the nerves (*Steinke, 2005, von Haller, 1936*). The Swiss physiologist reached this conclusion after carrying out over two hundred experiments on animals and reported his results in the book *On the Irritable and Sensible Parts of the Body* (*Wickens, 2015*).

Neurological observations on priapism from spinal cord injuries were the basis of understanding this disease since ancient times. Once with the advancement of neurology and neuroscience on the European continent, since the end of the 18th century, the first neuronal mechanisms which led to the understading of these entities were discovered and they opened the perspective of new corridors in the investigation on neurophysiological mechanisms (*Turliuc et al., 2018a*).

# I.4. Interdisciplinarity: neurosurgical approaches in ophthalmology, otorhinolaryngology, maxillofacial surgery and neuroanatomy

## I.4.1. Neurosurgical approaches in neuro-opthalmology: the sellar region

### I.4.1.1. Studies related to optic chiasm and its importance in neurosurgery

***Background***

Optic chiasma is an X-shaped structure located at the cranial base, representing the link of four important medical-surgical branches: neurosurgery, neurology, ophthalmology and endocrinology (*Glaser, 1999*). Throughout the ages, this structure, essential for for the sense of sight, incited anatomists and physicians, who have become extremely interested in finding out the truth about its structure and function.

*In the field of neuro-ophtalmology, I was interested in the sellar region, in clinical neuroanatomy and its implications in neurosurgery. The results have been published in a journal indexed in ISI Web of Science and 1 in international databases and the summary of the most important data are presented here, in the followings:*

Costea CF, Turliuc S, Buzduga C, Cucu AI, Dumitrescu GF, Sava A, **Turliuc MD**. *The history of optic chiasm from antiquity to the twentieth century.* Child's Nervous System 2017, 33(11):1889-1898. (Impact Factor in 2017 = 1.235)

*This article has 5 ISI citations.*

Cucu AI, Costea CF, Dumitrescu GF, Turliuc S, Sava A, **Turliuc DM.** *Ancient history of pituitary stalk*. Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology 2018, 17(1):83-86.

***Methods***

We have studied the entire medical literature on the optic chiasm, written by various authors from antiquity to nowadays (*Costea et al., 2017*).

***Results***

*Ancient theories about the optic chiasma; the first case-report of traumatic optic nerve injury after cranio-facial trauma*

Since ancient times, Hippocrates (c. 460-370 BC) anticipated the role of the optic chiasma, suggesting its role in vision (*Sarkies, 2004*). Moreover, he made the first description in the field of neuro-ophthalmological trauma, a first case-report of posttraumatic optic nerve injury after head injury: *"dimness of vision occurs in injuries to the brow and in those placed slightly above. It is less noticeable the more recent the wound but as the scar becomes old so the dimness increases"*

(*Chandwick and Mann, 1950, Costea et al., 2017*).

After Hippocrates, Rufus from Ephesus (80-150) was captivated by the sellar region anatomy. He performed necropsies on monkey (*Ellenbogen et al., 2012)* and not only described the anatomy of the chiasma or optic nerves, but he was also the first that understand the anatomy of the ventricular system and relations with optic chiasm (*Goodrich, 2012*, *Howard, 2012*). Moreover, Rufus was the first anatomist who introduced the term of *infundibulum* (Figure 75) in Terminologia Anatomica (*Cucu et al., 2018d*), comparing the funnel shape of the inferior part of the third ventricle with the huge leather bag used by Romans to transport wine which was called *infundibulum* (*Scatliff and Clark, 1992*).

Later on, Galen of Pergamon noticed this neuroanatomical structure criss-crossed in various animals, especially monkeys, which he named *chiasma*, due to resemblance with Greek letter *chi* (*Finger, 1994*, *Paluzzi et al., 2012, Costea et al., 2017*).

*Optical chiasm neuroanatomy in the Middle Ages*

Medieval Arab physicians did not make significant changes to Galenus and his predecessors' ideas, however, the physician and philosopher Rhazes (ca. 865-925) considered that optic nerves cross completely at the level of the chiasm (*Lindberg, 1976*).

*13th century theories regarding the optic chiasm*

In 1316, the anatomist and surgeon Mundinus de Luzzi (c. 1270-1326) in the first modern anatomical dissection manual (Figure 72) represented optic nerves mentioned by *D* that came from cerebral ventricles and intersected, naming the optic chiasma the common station for optic nerves (*de Luzzi, 1316, Swanson, 2014, Costea et al., 2017)* (Figure 73).

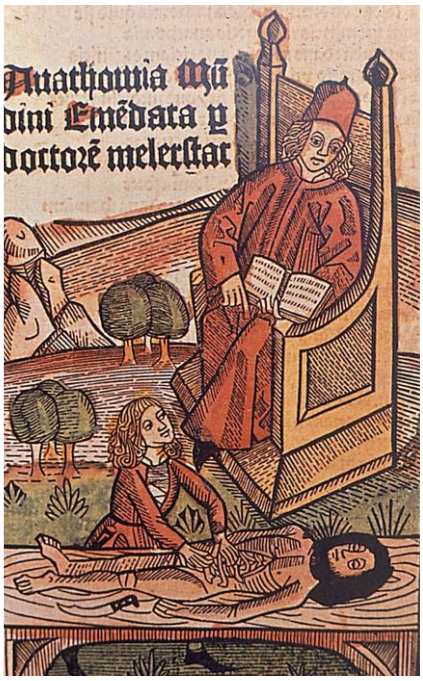

**Figure 72**. Frontispiece of Mundinus de Luzzi's *Anathomia corporis humani (1316),* (*De Luzzi, 1316*). (public domain)

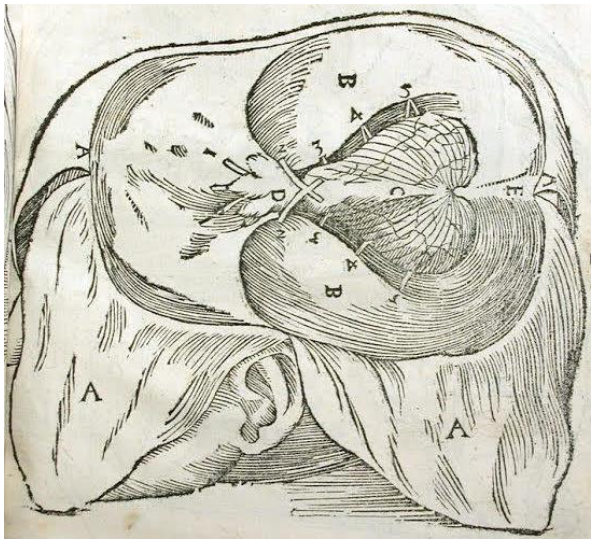

**Figure 73**. The representation of the optic chiasm by Mundinus de Luzzi in *Anathomia corporis humani (1316),* (*De Luzzi, 1316*).(public domain)

The first great medical illustrator, Leonardo da Vinci (1452-1519) drew the first diagram of cranial nerves, including of the optic chiasma, as well as the brain three-dimensional model, the wax casting of the cerebral ventricles with the earliest anatomical 3-D reconstructions (*Goodrich, 2000, Goodrich, 2012, Mortazavi et al., 2014, Costea et al., 2017*). Thanks to these models of the brain and visual apparatus, da Vinci is considered to be the one who has accurately approximated neuroanatomical relations with the chiasma (Figure 74). Beyond the role that he believed the optical chiasma had in vision, he also considered it to be important for the conjugated movements of the eyeballs (*Howard, 2012, Wade, 1999*).

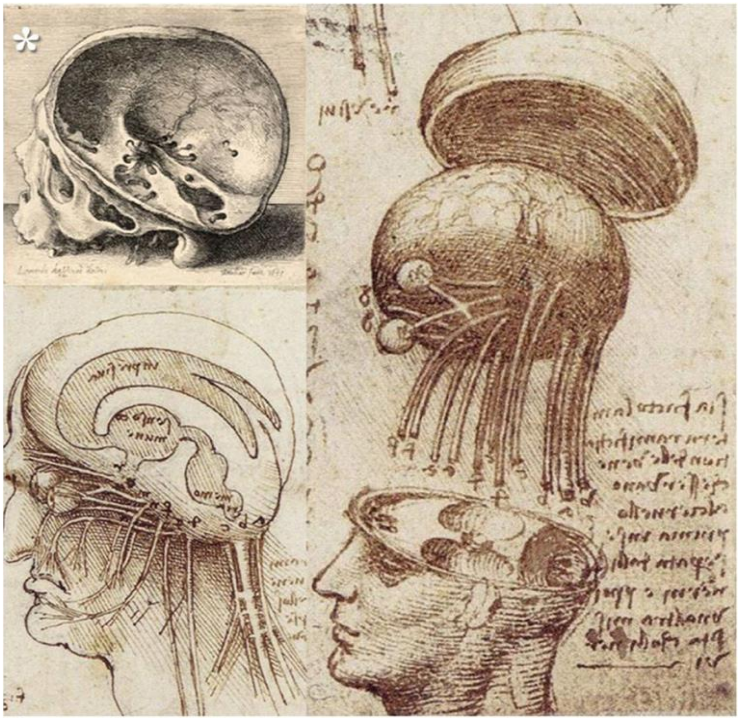

**Figure 74**. Da Vinci's vision of the optic chiasma (asterisk indicates the reprint of *Leonardo da Vinci of Wenceslaus Hollar, 1607–1677*) (from *Costea et al., 2017*). (public domain)

*The 15th and 16th centuries*

During the Renaissance, the Italian Bartolomeu Eustachio (1524-1574) was the first who founded the right anatomical route of the optic nerves and their relation with the optic chiasm. He supported the idea that the optic nerve does not project in lateral ventricles as ancients considered, but first crossing to the posterior part of the thalamus. Unfortunately, Eustachio's discovery was neglected for 150 years (*Howard and Rogers, 1995, Costea et al., 2017*).

Eustachio was followed by the famous anatomist Andreas Vesalius (1514-1564) who also described with great accuracy the neuroanatomy of the integral sellar region (*Costea et al., 2018*) and drew the optic chiasma in 1543 which he named *visoriorum nervorum coitus* (*Swanson, 2014*) (Figure 76). Furthermore, Vesalius also described two cases of anatomical anomalies in which the optic chiasm was absent and the optic nerves did not cross the opposite side (*Rucker, 1958*).

Furthermore, Vesalius also described the pituitary gland, which he called *glandula pituitam cerebri excipiens* (*Abderhalden, 1951, Medvei, 1982*), but also the *infundibulum*

which he called *basinor pelvis* (Figure 75), and he stated that it *"is shaped like a funnel […] that receives the cerebral pituita that flows down from the third ventricle […] and […] through which cerebral pituita drips into the gland through foramina next to the gland"* (*Vesalius et al., 1543/2009*).

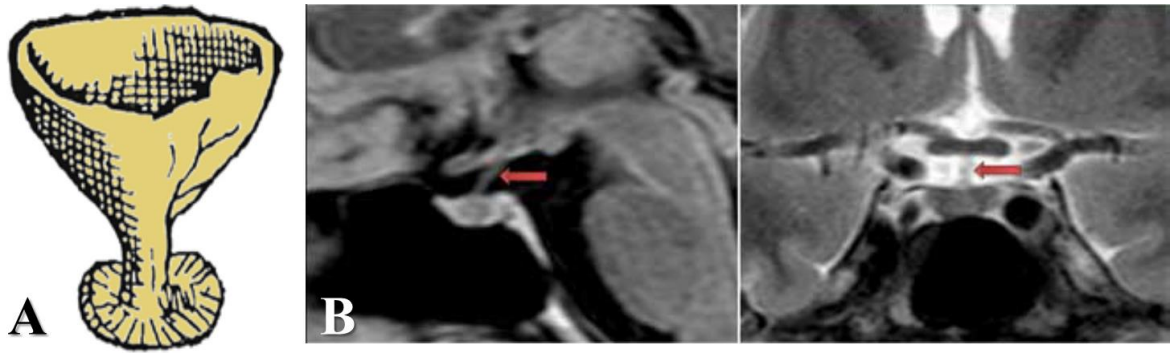


**Figure 75**. Vesalius's drawing of the *infundibulum* (adapted from *De Humani Corporis Fabrica, 1555*) (A). MRI aspect of pituitary stalk (red arrows) (*Dr. A. Cucu's personal collection*) (B). (from *Cucu et al., 2018d*)

Several years later, in 1573, the anatomy professor Costanzo Varolio (1543-1575) proposed a new dissection method of the brain, not like it had been done before, from the upper part down, but through the detachament of the brain from the skull base (*Tubbs et al., 2008*). Naturally, the results of this new type of dissection did not fail to appear and Varolio visualized the optic chiasm and the visual system much better, describing them in detail and drawing them in his book *"De nervis opticis nonnullisque aliis, praeter communen opinionem in Humano capite observatis (On the optic nerves observed in the human brain and a few other particulars adverse to the common opinion)"* (*Sarkies, 2004, Costea et al., 2017*). By implementing this new method of dissection, Varolio is considered to be the first neuroanatomist who discovered the entire optic nerves trajectory, from origins to their ending (*O'Malley, 1980*) (Figure 76).

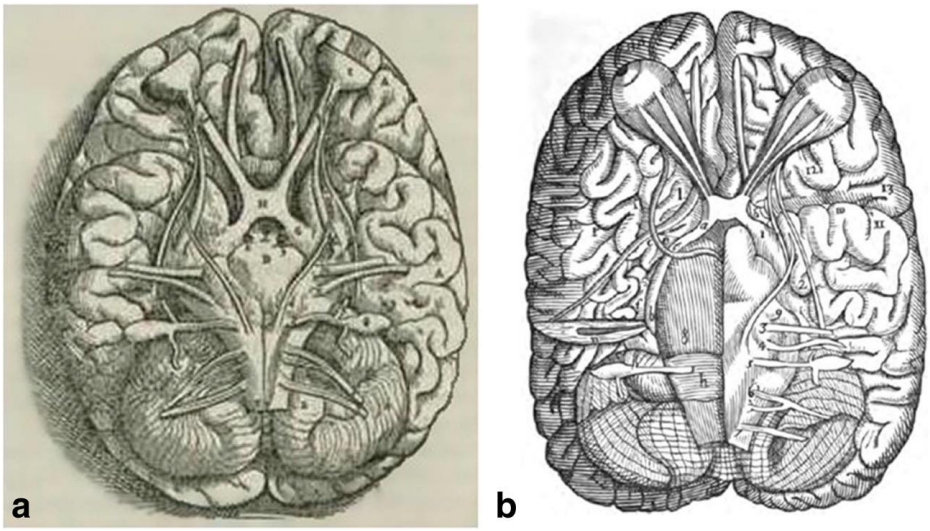


**Figure 76**. The optic chiasma drawn by Andreas Vesalius (a) and Costanzo Varolio (b). (public domain)

The rector of the medical school of Montpellier, Andre du Laurens (1558-1609) was the one who recommended the name *chiasma opticum* in anatomic language, in 1595 (*Prioreschi, 2007*).

Until the 17th century, the optic nerves decussation of was mostly established on speculations and controversy. In 1682, the one who mentioned that the optic nerves in fact partially cross the chiasma was the mathematician Isaac Newton (1642-1727) (*Briggs, 1809*).

With the construction of modern hospitals in the old continent at the beginning of the 18th century (Figure 77), physicians have begun to increasingly integrate theoretical notions about optic chiasma. Thus, in 1718, Jean Louis Petit (1674-1750), the initial chief of the *Academie de Chirurgie* in Paris (Figure 78) was among the first to describe the visual deterioration caused by pituitary enlargement (*Medvei, 1982, Petit, 1718*).

**Figure 77**. 1820 Engraving of Guy's Hospital Entrance in London, one of the first voluntary hospitals established in 1724 *(Engraver William Woolnoth (1785-1836)*. (public domain)

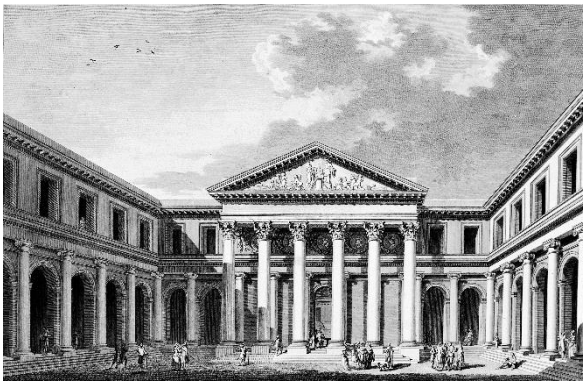

**Figure 78**. Academie de Chirurgie, Paris. (public domain)

Later on, the Germans Christian Heinicke and Abraham Vater were the first to explain this phenomenon of *halved vision*, applying in clinical neuro-ophthalmology the theory of semidecussation of the optic nerves at the level of the chiasma (*Vater and Heinicke, 1757*).

In the late of the 18th century, the anatomist Félix Vicq D'Azyr (1748-1794) performed brain slices in different plans, identifying the real retrochiasmal optic pathways, including chiasma and optic tracts (*Vicq D'Azyr, 1786, Costea et al., 2017*).

In 1824, the physicist and chemist William Wollaston (1766-1828) presented his medical experience with homonymous hemianopsia in front of the general assembly of the Royal Society of London (*Lebensohn, 1941*). Unfortunately, 4 years later, he died of a cerebral tumor and the postmortem examination demonstrated the existence of a tumor in the right thalamus, *"as large as a hen's egg"* (*Simpson and Crompton, 2008, Costea et al., 2017*).

The 19th and 20th centuries were marked by experimental studies, carried out especially on the nervous system, and these led to the development of the anatomical and physiological notions of optic chiasm. One such example is Albrecht von Graefe (1828-1870), who published in 1856 an important reference for the field of neuro-ophthalmology, in which he described binasal hemianopia, bitemporal hemianopsia and homonymous hemianopsia (*von Graefe, 1856*). He was followed by the Italian neuropsychiatrist Andrea Verga (1811-1895) who discovered in 1864 at a necropsy on a

female patient the presence of a pituitary adenoma which compressed the chiasm and eroded the sinus of the sphenoid bone, causing visual impairment (*Maartens, 2005*).

The 20th century was marked by Santiago Ramón y Cajal's experimental studies (Figure 79), who discovered in the mammalian chiasm that some axons crossed the opposite side in the optic chiasma, while some did not, remaining on the same side (*y Cajal, 1911, y Cajal, 1899*) (Figure 79).

The ophtalmologist Hermann Wilbrand (1851-1935) discovered simultaneous the *Wilbrand's knee* at the level of the chiasma (*Costea et al., 2017, Simpson and Crompton, 2008,*), and after the 1950s, data about the optic chiasm was concluded after performing experiments on macaque monkeys by various authors (*Hoyt and Luis, 1962, Polyak, 1957*).

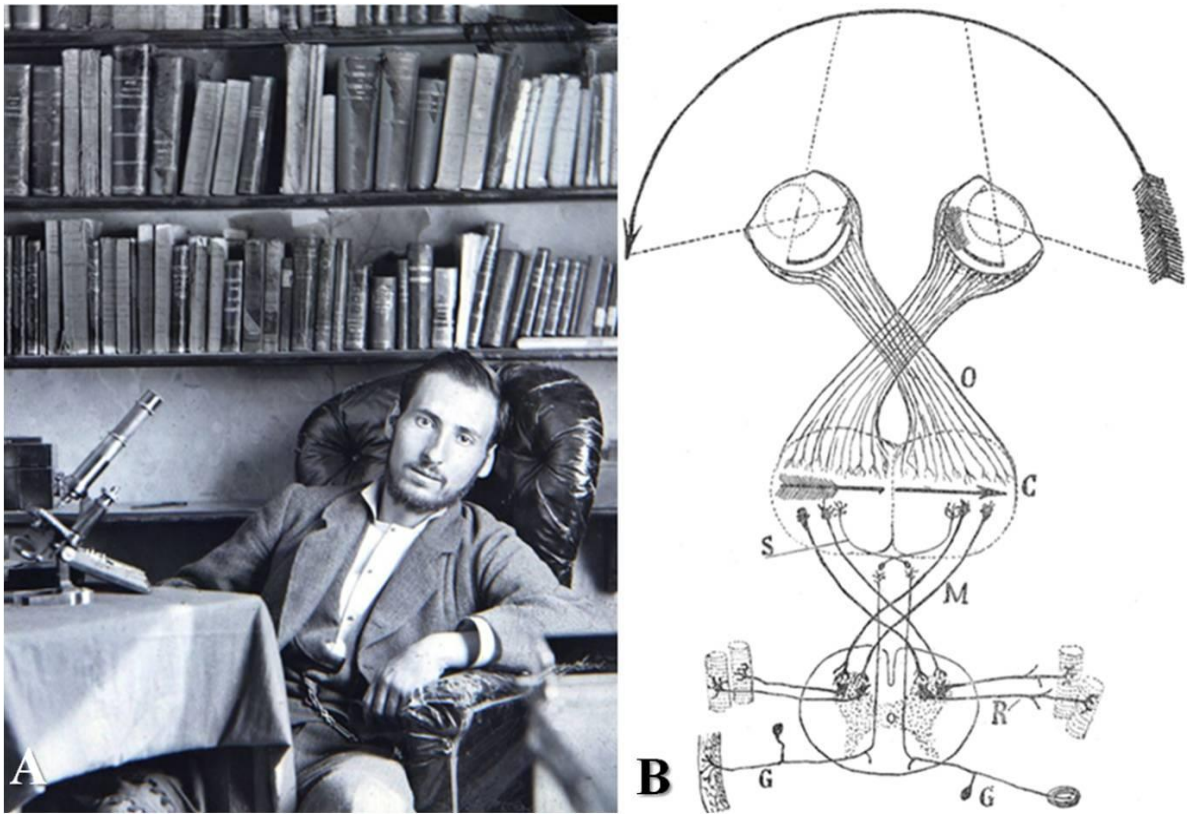


**Figure 79**. Santiago Ramón y Cajal (1852-1934) (A). Schematic illustration of the chiasm, by Santiago Ramón y Cajal (B). (from *Costea et al., 2017*). (public domain)

To conclude, it is important to have knowledge of the evolution over time of various theories on the anatomy and function of optic chiasm, all the more so as these have led to the occurence of new disciplines, such as neuro-ophthalmology (from *Costea et al., 2017*).

### I.4.1.2. Controversy in the field of neuro-ophthalmology: Wilbrand's knee - does it exist?

*In 2018, upon the request of Prof. Dr Concezio De Rocco, President of the International Society for Pediatric Neurosurgery and the European Society for Pediatric Neurosurgery and Editor-in-Chief of the Child's Nervous System journal, we published an article (letter to editor) regarding the presence of Wilbrand's knee and summary of the most important data is presented here, in the*

*followings:*

Costea CF, Turliuc S, Cucu AI, **Turliuc MD**. *To be or not to be Wilbrand's knee? A question that is looking for an answer.* Child's Nervous System 2018, 34(11):2135. (Impact Factor in 2018 = 1.235)

This article has 2 citations.

In the 19th century, the German-born ophthalmologist Hermann Wilbrand (1851-1935) (Figure 80) noticed that in the chiasma, the nervous fibres from the lower retinal quadrants loop forward into the termination of the contralateral optic nerve before going back in the optic tract (*Wilbrand, 1926, Costea et al., 2018a*) (Figure 81).

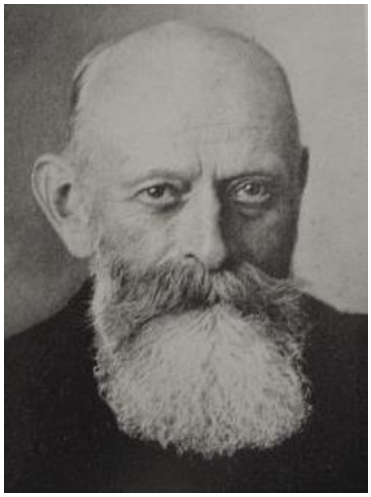

**Figure 80**. Hermann Wilbrand (1851-1935) (public domain)

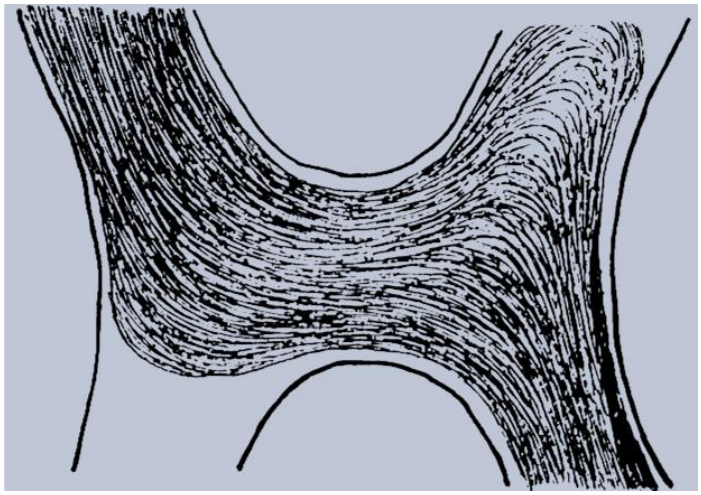

**Figure 81**. Final anatomic drawing by Wilbrand of his "knee" (adapted *after Wilbrand, 1926*)

In 1997, Horton demonstrated that optic nerve fibers cross the optic chiasm without going to the controlateral optic nerve (*Horton, 1997, Costea et al., 2018a*), his study being later complemented by Lee *et al.* who reached the same conclusion (*Lee et al, 2006b*). These are the only two studies that challenged the presence of Wilbrand's knee, considering it at the same time an artifact (*Costea et al., 2018a*).

Nonetheless, later, in 2014, Shin *et al*. succeeded in demonstrating the presence of Wilbrand's knee, using anisotropic light-reflecting properties of myelinated axons. The conclusions were based on the analysis of thin sections of the chiasm of 25 μm which authors illuminated and digitally imaged from distinct angles, visualizing nervous fibres consistent with Wilbrand's original description (*Shin et al., 2014, Costea et al., 2018a).*

In 2016, the researchers from Georgetown University and the University of Maryland proved on three monkey and four human optic chiasms that, in all cases of human optic chiasms, there are thin fiber tracts that correspond to Wilbrand's knee. Moreover, such tracts could not be found in any of the three monkey chiasms, the researchers reporting that Wilbrand's knee founds in humans and are not found in monkeys (*Kachhela, et al., 2016, Costea et al., 2018a*).

Considering the dispute in the literature regarding the presence of Wilbrand's knee, we

believe that, despite conflicting reports, the professor of ophthalmology Hermann Wilbrand is worth mentioning in all paper on the history of neuro-ophthalmology, for his important concept – Wilbrand's knee, and for what professor means: one of the beginnings of modern neuro-ophthalmology (*Costea et al., 2018a*).

### I.4.1.3. Case series and review of literature on neurosurgical pathologies of the sellar region

***Background regarding fibrous dysplasia***

Fibrous dysplasia (FD) is a rare disease, characteried through bone mass expansion (*Abe et al., 2002*) and developed in 71.9-86% of the cases of postzygotic activating mutations of the GNAS gene on chromosome 20q13 (*Schwindinger et al., 1992, Tabareau-Delalande et al., 2013, Weinstein et al., 2002, Costea et al., 2015*). It can have two forms of presentation, affecting a single bone or multiple bones.

As regards the prevalence of the FD in the craniofacial skeleton, the data in the literature are inconsistent, with reports varying between 10-25% in monostotic form and up to 90% in polyostotic form (*Ricalde et al., 2012*).

FD lesions are typically manifested in the first period of life and develop mostly in childhood and adolescence, and bone lesions with clinical significance become apparent around the age of 5 (*Burke et al., 2017*). In some cases, lesions from FD can become less active in adulthood, and could be linked with apoptosis of mutation-bearing BMSCs (*Kuznetsov, et al., 2008*). In a study, Hart *et al*. demonstrated that 90% of craniofacial FD lesions have been depicted at an average age of 3.4 years (*Hart et al., 2007*).

When it comes to visual impairment in orbitofrontal sphenoidal FD, the visual impairment is progressive, caused especially by bone excrescence and compression of the optic nerves (ONs) and can occur in up to 50-90% of the cases (*Katz and Nerad, 1998, Costea et al., 2015*), and could also be produced by sphenoid sinus mucocele (*Sharifi et al., 2013*).

Costea CF, Cucu A, Costan VV, Dumitrescu GF, Sava A, **Turliuc D**. *Visual impairment in orbitofrontal and sphenoidal fibrous dysplasia associated with sphenoid sinus mucocele*. Journal of Clinical Research and Ophtalmology 2015, 2(4):054-057.

***Case report***

In the article mentioned above, we have reported the case of a young male patient, aged 20, admitted to the Department of Neurosurgery at *Prof. Dr. Nicolae Oblu* Clinical Emergency Hospital Iași for facial deformity, headache and sudden decrease in visual acuity of both eyes over the past month. We discovered, from his medical history, that he had a progressive visual impairment in the right eye for the past years. The ophthalomological examination highlighted in the right eye - hand movements, and best corrected visual acuity of the left eye - 20/60. Furthermore, we noticed an optic disc atrophy in the right eye and a normal optic disc in the left eye. Imaging explorations advocated for the diagnosis of monostotic craniofacial FD associated with mucocele of the sphenoid sinus, causing partial obliteration of the bilateral optic canals (*Costea et al., 2015*) (Figure 82).

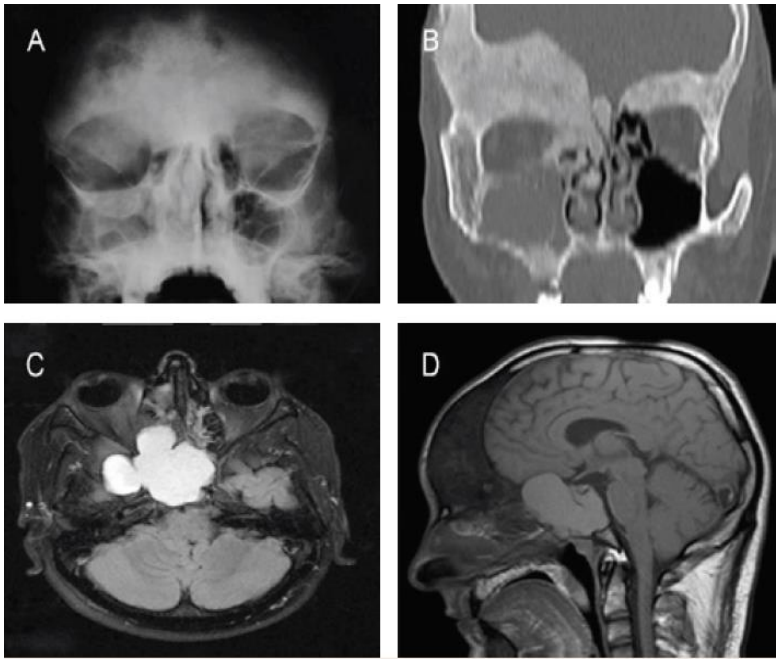


**Figure 82**. "Orbitofrontal and sphenoidal fibrous dysplasia: characteristic aspects of "ground glass" (A). CT scan appearance (B). MRI scan appearance: homogeneous well defined cystic lesion located in the sellar, suprasellar and parasellar areas", with compressive effect on the optic chiasm (C). T1WI showing the large cyst and frontal dysplasia (D) (from *Costea et al., 2015*)

The patient underwent two successive surgeries: the first one was carried out for the bilateral decompresion of the ONs, and the second for the evacuation of the large sphenoid sinus mucocele through a transfacial and transmaxillary approach *(Costea et al., 2015*) (Figure 83).

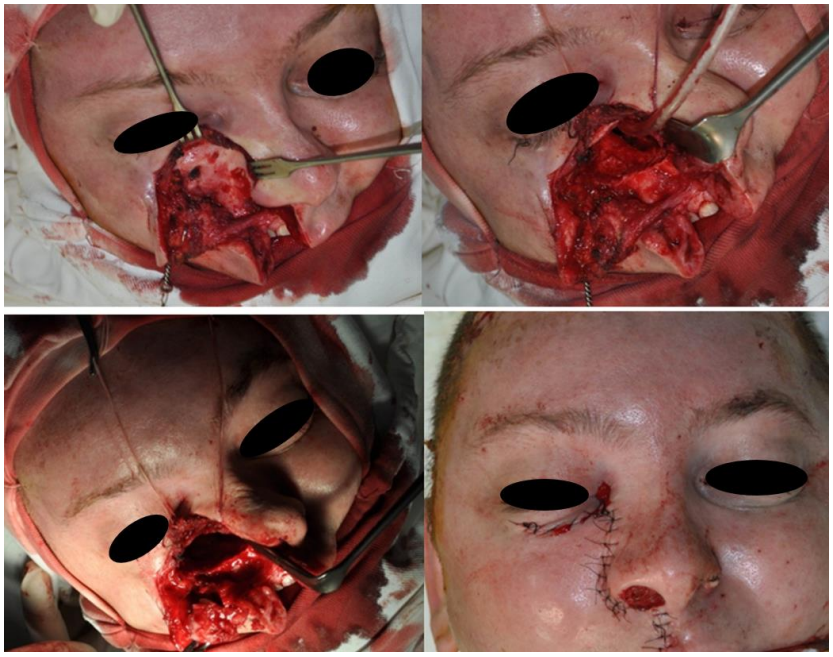

**Figure 83**. Intraoperative and postoperative views - transmaxillary approach (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

The anatomopathological diagnosis confirmed the diagnosis of FD (Figure 84 and 85).

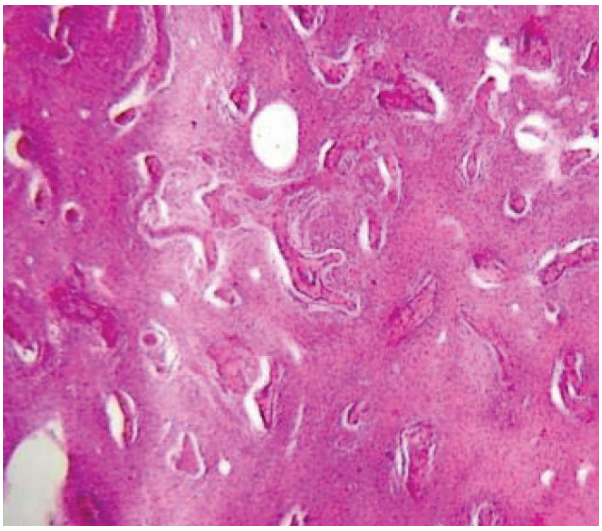

**Figure 84**. "Fibrous dysplasia: normal bone was replaced with newly formed bone trabeculae, thin, irregular-looking like "Chinese letters", separated by fibrous connective tissue (HE, x40)". *Courtesy of Dr. G. F. Dumitrescu* (from *Costea et al., 2015*)

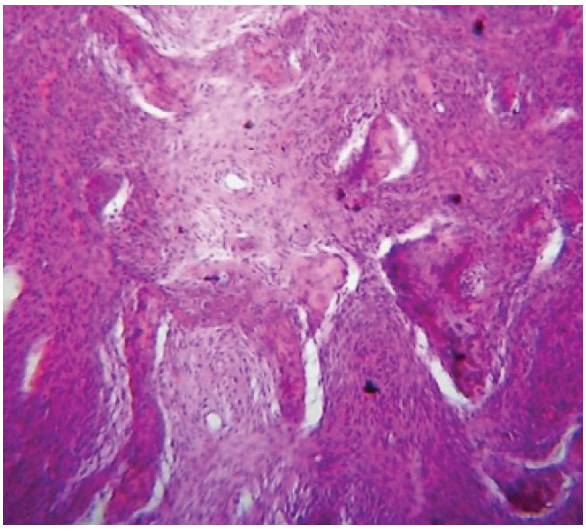

**Figure 85**. "Microscopic field with lens of higher power highlights immature bone blades, poorly calcified bone pattern and with the presence of osteoblasts only from place to place. Form of the newly formed bone blades ranging from small oval islands, curves or serpinginiouse, which gives the impression of "Chinese letters" or "alphabet soup" (HE, x100)". *Courtesy of Dr. G. F. Dumitrescu* (from *Costea et al., 2015*)

Regarding the craniofacial involvement in monostotic FD, the maxillozygomatic complex is the most common (*Lee et al., 2002*), the frontal and sphenoid bones being rarely involved (*Araghi and Haery, 1993*).

Furthermore, in orbitofrontal sphenoidal FD, the decrease of visual acuity is encountered in 50-90% of the cases and is realized by progresive osseous proliferation and compresion of the ONs (*Katz and Nerad, 1998*). In this case, the impairment of the visual function of both eyes initially occurred due to the progressive compression of the optic canals, predominantly on the right side because of the FD, and later due to the supplementary compression of the right optic nerve (ON) and optic chiasm by a large sphenoid sinus mucocele. After the evacuation of the mucocele, left eye visual acuity was completely recovered (*Costea et al., 2015).*

In FD, surgery is a controversial treatment and consists in the decompression of ONs, preventive or therapeutic (*Abe et al., 2002, Chen et al., 1997, Edgerton et al., 1985, Papay et al., 1995*). In our case, the first surgical treatment was intended to decompress the bilateral ON, while the second surgery was for the mucocele evacuation of the sphenoid sinus compressing both ONs nerves as well as the optic chiasm.

To conclude, in the case presented, the diagnosis of FD was established late, when the patient was admitted for bilateral visual acuity impairment and also for cefalalgia and craniofacial

abnormality. Furthermore, ONs and chiasma compression was due both to orbitofrontal FD and a large sphenoid sinus mucocele, two entities that involved the visual apparatus (*Costea et al., 2015*).

***Background regarding arachnoid cyst***

The arachnoid cyst (AC) is a congenital collection of cerebrospinal fluid (CSF) between an arachnoid membrane and the subarachnoid space (*Lemire et al., 1975, Rengachary, 1981, Rengachary and Watanabe, 1981, Turliuc et al., 2016a*).

The first case of AC was reported in 1831 by the physician Richard Birght (1789-1858), and the lesion was in the temporal cranial fossa (*Pradilla and Jallo, 2007*). The incidence of AC currently varies between 0.2 and 1.7% (*Morris et al., 2009, Vernooij et al., 2007, Weber and Knopf, 2006, Katzman et al., 1999, Eskandary et al., 2005*), although there are studies reporting a higher incidence, namely 2.6% (*Al-Holou et al., 2010*).

Nowadays, most arachnoid cysts (ACs) are diagnosed incidentally, when performing neuroimagistics for mild head injuries (*Rajendra et al., 2012*).

Although they are usually single, in rare cases, ACs may be multiple or bilateral, some authors even reporting family occurrences (*Handa et al., 1981, Pradilla and Jallo, 2007, Jamjoom et al., 1995, Wester, 1992*). As concerns sellar region ACs, they make up about 3% of all intracranial ACs (*Rengachary, 1981, Rengachary and Watanbe, 1981*).

**Turliuc DM**, Cucu AI, Dobrovăț B, Trandafir D, Turliuc S, Dumitrescu GF, Costea CF. *A rare case of suprasellar arachnoid cyst with giant perimesencephalic and mesial temporal extension-physiopathological mechanisms*. Romanian Neurosurgery 2016, 30(1):52-56.

***Case report***

Another case with sellar region involvement was that of a 34-year-old man with a suprasellar AC with giant perimesencephalic extension. He came to our hospital complaining of right hemicrania-like migraine and neurotic syndrome, as well as subjective neurovegetative symptoms. The head CT scan revealed a sharp and non-enhancing extra-axial cyst, with cerebrospinal fluid density, located at the level of the basal cisterns and medial bilateral temporal lobes. The neuroimaging exploration was followed by a MRI scan, which revealed even better a large and relatively symmetrical cyst in the temporal cranial fossa, which followed the CSF signal on all MRI sequences (*Turliuc et al., 2016a*) (Figure 86 and 87).

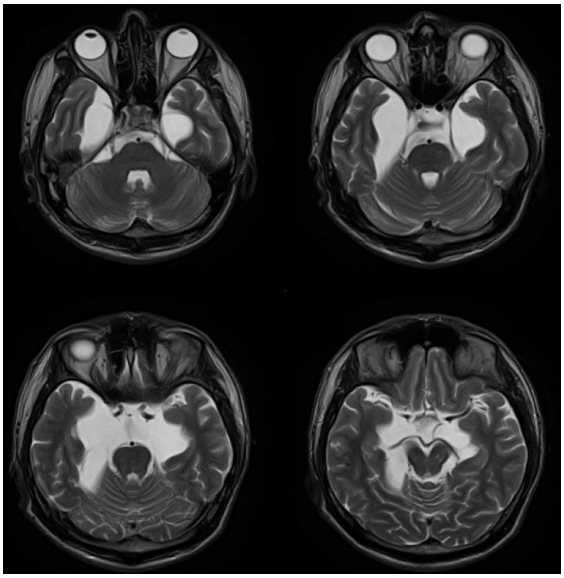

**Figure 86**. The temporal cranial fossa contains large and relatively symmetrical cystic lesions (from *Turliuc et al., 2016a*)

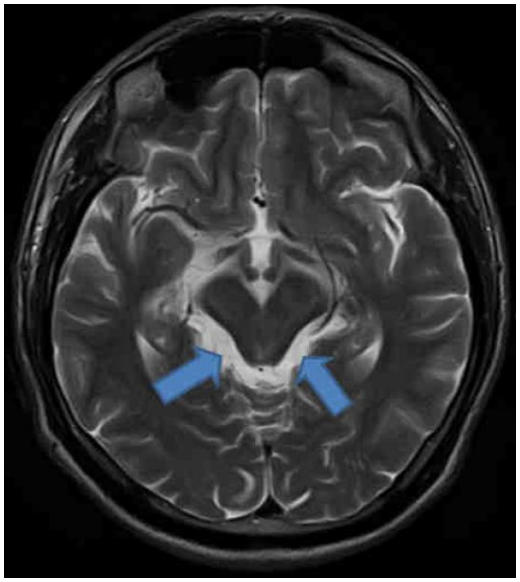

**Figure 87.** Symmetrical enlargement of ambient and quadrigeminal cisterns (blue arrows) (from *Turliuc et al., 2016a*)

As far as the physiopathological mechanisms of AC occurrence are concerned, some authors (*Fox and Al-Mefty, 1980, Sansregret et al., 1969*) argue that the membrane of Liliequist would play an important role in the occurrence and development of the suprasellar AC. Whereas this membrane is normally perforated, in some cases it may be imperforated, either as a result of a congenital development, or due to an acquired adhesive arachnoiditis accompanied by CSF obstruction from subtentorial to supratentorial subarachnoid spaces (*Fox and Al-Mefty, 1980, Turliuc et al., 2016a*). Thus, continuous CSF flow from fourth ventricle to posterior spinal subarachnoid space and then to anterior spinal subarachnoid space will cause an upward expansion of the membrane of the suprasellar cistern, then a progressive dilatation of the suprasellar cyst with extension to the basal cisterns (Figure 86) and next into the crural and carotid cisterns with widening of the subarachnoid spaces of the infero-medial area of the temporal lobe (*Gentry et al., 1986, Turliuc et al., 2016a*).

In conclusion, as far as we know, this case of suprasellar AC with large perimesencephalic and medial temporal extension is the first case of this type reported in literature. Note the discrepancy in this case between neuroimaging and nonspecific symptomatology. If neurological symptoms are absent, our recommendation is only for neuroimaging follow-up, as improperly recommended surgery would result in pressure imbalance between the multiloculated spaces (*Turliuc et al., 2016a*).

### I.4.2. Researches regarding malignant sinonasal tumors with intracranial extension

***Background***

The use of combined craniofacial resection in sinonasal malignant tumors extending to the anterior cranial base improved outcomes for patients (*Mine et al., 2011*). Nevertheless, the poor prognosis in the case of malignant sinonasal tumors is mainly due to their local extension in the skull base (*Suarez et al., 2004*).

Despite the more aggressive surgical approaches to these types of diseases have been lately developed, due to the complex anatomy of the region and to their low occurrence rate, these tumors still raise diagnostic and therapeutic challenges (*Kawaguchi et al, 2017*).

Costinescu V, Palade OD, Stegaru G, **Turliuc D**, Grigoras M. *Combined endo- and extracranial approach for the sinonasal tumors invading the anterior skull base.* Revista Medico-chirurgicală a Societății de Medici și Naturaliști din Iași 2003, 107(3):110-115.

We report the case of a 40-year-old man who was admitted to *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital with a giant facial tumor (Figure 88), complete bilateral nasal obstruction, bloody rhinorrhea and recurrent bilateral anterior epistaxis, which had been progressing for about 6 months.

The anterior rhinoscopy revealed a tumor in the right nasal fossa, whereas posterior rhinoscopy revealed the presence of a polypus in the right choana and the top of the rhinopharynx pushed by the tumor.

The specificity of this case consisted of the fact that, despite the giant size of the tumor and significant extension to the neighboring structures (Figure 88), at the time of admission, the patient did not show any neurological symptoms or paralysis of the extraocular muscles. The CT scan revealed a giant mass in the nasal fossae, in the whole right maxillary sinus, partly in the left maxillary sinus and in the sphenoid sinuses. The CT scan also revealed orbit and front sinus invasion and posterior extension in the anterior skull base (*Costinescu et al., 2003*) (Figure 89).

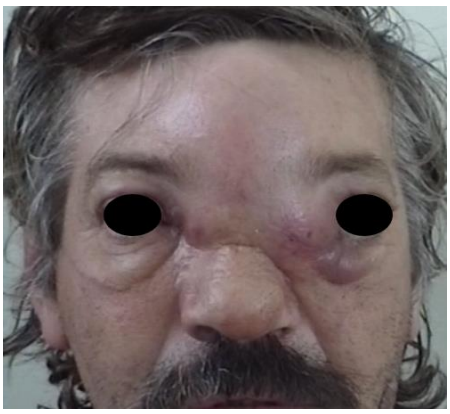

**Figure 88**. Preoperative image (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

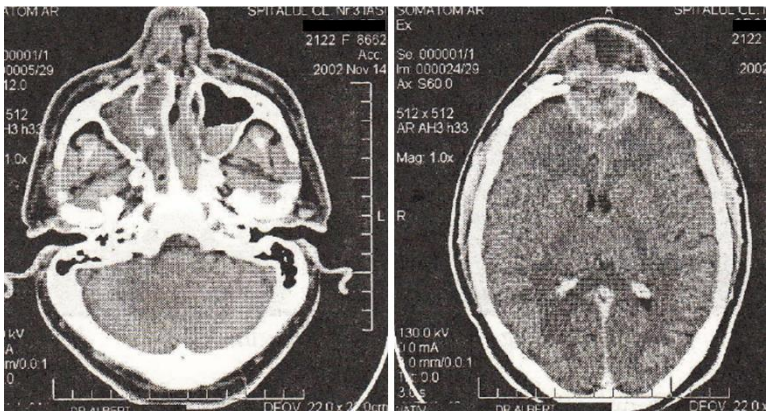

**Figure 89**. Head CT scan showing tumor with intracranial extension (from *Costinescu et al., 2003*)

The surgical procedure (Figure 90 and 91) consisted of tumor resection by atypical mixed cranio-frontal and medio-nasal approach, after placing a waiting thread on the right external carotid artery. During surgery, we noted that the tumor was not extending to the eyeballs or the dura mater, and thus we manage to detach the tumor from these anatomical structures. The final histopathological diagnosis was nonkeratinizing epidermoid carcinoma with extensive necrotic areas. After surgery, the patient underwent chemotherapy and 30 days after the surgery, external radiotherapy was initiated. The patient's evolution was positive, as no immediate, 1, 6 or 12 month relapse occurred

(*Costinescu et al., 2003*).

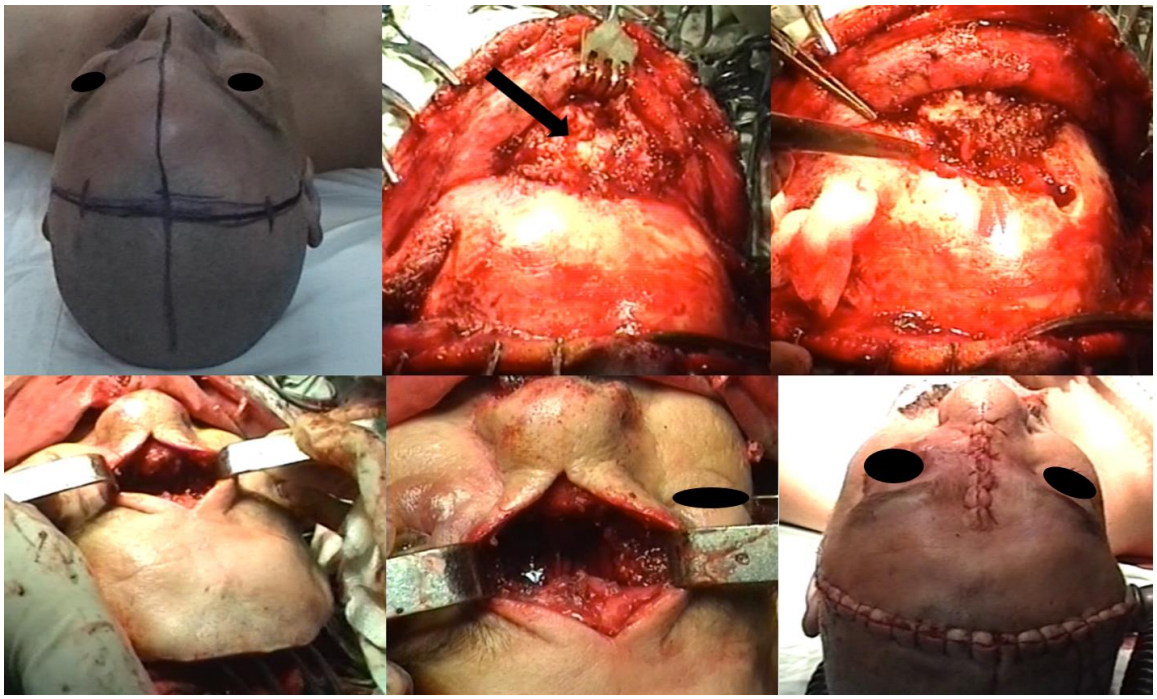

**Figure 90**. Preoperative, intraoperative and postoperative images (black arrow – extracranial extension of the tumor) (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

In the case of sinonasal tumors, each case must be individualized from the point of view of its therapeutic approach and it must be assessed by a complex multidisciplinary team including an oncologist, a radiotherapist and a surgeon. In our opinion, the mixed surgical approach (neurosurgeon-ENT specialist) to malignant tumors invading the anterior floor of the skull base is the only way to achieve complete tumor resection (*Costinescu et al., 2003*).

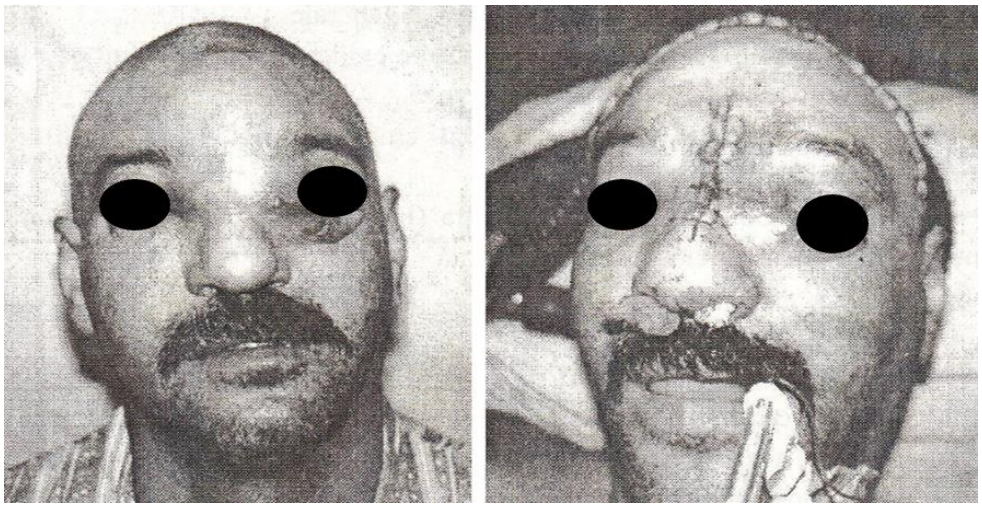

**Figure 91**. Preoperative and postoperative images (from *Costinescu et. al., 2003*)

### I.4.3. Research on orbital tumors in adults

***Background regarding orbital tumors***

Tumors occurring in the orbit are still a challenge nowadays, not only due to the complex anatomy and to the multitude of neighboring anatomic structures, in which the tumor development may have originated, but also to the complex imaging, diagnosis and management requirements (*Darsaut et al., 2001*).

In a large case study on 1264 patients with suspected orbital tumor or tumor-simulating condition, Shields *et al.* (*Shields et al., 2004*) noted that the most numerous were vasculogenic lesions (17% of the cases) followed by lymphoid, lacrimal gland tumors, optic nerve and meningeal tumors, metastasis, peripheral nerve tumors and primary melanoma lesions (*Shields et al., 2004, Tailor et al., 2013*).

Another specificity of these orbital tumors is their localization in an anatomic area where several medical specialties meet: neurosurgery, maxillofacial surgery, otorhinolaryngology and ophthalmology.

*I have published several original research papers on the topic of orbit tumor pathology, among which 1 paper in a journal indexed in ISI Web of Science and 2 papers in a journal indexed in other international databases. These papers prove the importance of the multidisciplinary approach to orbit tumors and the publications hereunder include the summary of the most important data:*

Ciofu ML, Sulea D, Nicolau A, Grigoras C, **Turliuc DM**. *Management of orbital tumors presenting as unilateral exophthalmos.* Romanian Journal of Oral Rehabilitation 2017, 9(4):66-72.

Costan VV, Sava A, Carauleanu A, Costea CF, Cucu AI, Dimitriu G, Dumitrescu GF, Dumitrescu N, Stoicescu MS, Raftu G, **Turliuc MD**. *Histopathological and clinical characteristics of surgically removed cavernous venous malformations (so-called cavernous hemangiomas) of the orbit.* Rev Chim (Bucharest) 2019, 70:350-354. (Impact Factor in 2018 = 1.605)

In a retrospective study conducted in cooperation with the Department of Maxillofacial Surgery at *Sfantul Spiridon* Hospital between 2012 and 2016, we monitored 17 patients with orbital tumors. We only included in the study patients who initially came in for proptosis.

Of the 17 patients, 9 were men and 8 were women, all between 23 and 74 years of age. Other additional complaints included: headache (*n=5*), hemifacial algia (*n=4*), visual disturbances (*n=3*), diplopia (*n=3*) and nasal obstruction (*n=6*). The initial examinations included a multidisciplinary approach, with ophthalmological examination in all the cases, neurosurgical examination in 13 cases and ENT examination in 7 cases. 3 of the 17 cases were primary orbital tumors and 1 tumor pertaining to the lacrimal gland.

Secondary tumors extended to the orbit were: 5 sinonasal tumors, 6 skin tumors and 2 anterior skull base tumors with orbital invasion. We performed biopsy prior to surgery in 7 cases (3 basal cell carcinomas, 2 squamous cell carcinomas, 2 lymphomas), and only 11 patients underwent surgery. 4

tumors were considered unresectable due to the extensive invasion of the intracranial space or of the internal carotid artery. We performed complete excision in all benign tumors (n=3), complete removal and orbital content preservation (n=8), orbital exenteration (n=2) and extended orbital exenteration (n=1) (*Ciofu et al., 2017*).

In our study, surgery was recommended after multidisciplinary evaluation. Thus, the biopsy was performed prior to surgery in cases where the tumor was accessible and did not have malignancy characteristics, and when choosing the surgical approach and reconstruction technique we first considered the incidence of postoperative sequelae, as orbital surgery involves a considerable risk of injury to important anatomical structures.

Our study has shown that a multidisciplinary surgical team consisting of neurosurgeon, maxillofacial surgeon and ophthalmologist is extremely important in the removal of skull base tumors extending to the orbit (*Ciofu et al., 2017*).

A second study on orbital tumors was conducted on a group of 14 patients with orbital cavernous hemangiomas, between 2010 and 2017. We considered the demographic data, symptoms and also radiological and surgical findings (*Costan et al., 2019*).

As concerns the findings, all the patients were women between 13 and 57 years of age (the mean age was 44.2 ± 5.7 years), and the main symptom was proptosis in 71.42% of the cases (*n=10*). In 28.57% of the patients (*n=4*), cavernous hemangioma was discovered by accident, on the occasion of an imaging exploration for cephalalgia. The left orbit was involved in 78.57% of the cases (*n=11*).

Surgical treatment consisted of anterior orbitotomy, because the lesions were located in the extraconal inferior or medial orbital compartments. Complete tumor resection was achieved in all patients and, six months after operation, the exophthalmos had decreased and no recurrence was noted (*Costan et al., 2019*).

In our patient group, we identified a mixture of venous muscular channels and capillary structures (Figure 92). They were separated by thick strands of connective tissue. We also identified in the walls of large vascular channels variable multilaminar smooth muscle-like bundles under the endothelium, similar to other authors (*Osaki et al., 2013*), the image most closely resembling dysplastic veins. As a result, we concluded that the so-called orbital cavernous hemangioma is rather a cavernous venous malformation (*Costan et al., 2019*).

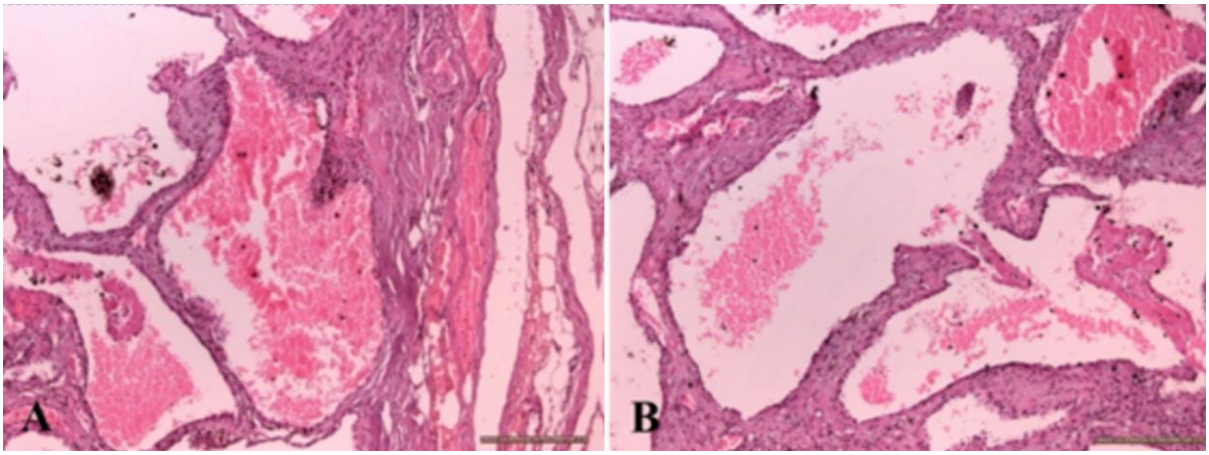


**Figure 92**. "Large cavernous vascular channels filled with blood and lined by a single layer of

flattened endothelial cells and separated by scant connective tissue stroma. A fibrous pseudocapsule surrounded the lesion (HE staining, x10) (A). The central part of the lesion showed large, endothelium-lined, blood-filled spaces, which are tightly knit and separated by thick septa (HE staining, x10)" (B) *Courtesy of Dr. G. F. Dumitrescu,* (from *Costan et al., 2019*)

Our study has shown that orbital cavernous hemangiomas usually occur in women and have the clinical-imagistic expression of a benign lesion. We recommend that surgery be recommended in the case of symptoms such as diplopia, proptosis or exophthalmos. Also, immunohistochemical diagnosis is of great help and we conclude that so-called orbital cavernous hemangiomas are rather cavernous venous malformations. Since we have identified nests of microcapillary networks in the interstitium of these lesions, we consider these histopathological characteristics as the proof of their slow, but progressive growth (*Costan et al., 2019*).

***Background regarding periocular and orbital basal cell carcinoma***

Basal cell carcinoma (BCC) is still the most common eyelid neoplasia, making up about 80-90% of all periocular malignancies (*Lee et al., 1999a, Tesluk, 1985*); nevertheless, if the tumor is fully resected, the prognosis is good.

The most important factor contributing to the development of BCC is prolonged exposure to UV light and BCC typically occurres on sun-exposed body parts like the head, face and neck (*Rigel, 2008*).

Although BCC is thought to develop from progenitor cells residing in the intra-follicular epidermis (*Youssef et al., 2010*), the precise origin of this type of cancer has not been fully discovered (*Göppner and Leverkus, 2011*). To date, there is no homogeneous histological classification of periocular BCC, although 26 histopathological subtypes have been described so far (*Wade and Ackerman, 1978*).

Depending on the risk of recurrence, periocular basal cell carcinomas (BCCs) were divided into low-risk tumors (adenoid, nodular and basosquamous subtypes) and high-risk tumors (morpheaform subtype) (*Grostern, 2003*).

Costea CF, **Turliuc MD**, Sava A, Dimitriu G, Dumitrescu GF, Danca C, Cucu AI, Bogdanici CM, Costache II, Buzduga CM, Ciocoiu M, Tanase DM, Dragomir RA, Carauleanu A. *Periocular basal cell carcinoma: demographic, clinical histological and immunohistochemical evaluation of a series of 39 cases*. Romanian Journal of Morphology and Embryology 2019, 60(1):77-86. (Impact Factor in 2018 = 1.5)

*This article has 1 ISI citation.*

***Materials and Methods***

We conducted a retrospective study in which we have analyzed demographic, clinical, histopathological and immunohistochemical data in all cases of periocular excision specimens diagnosed as periocular BCC in the Department of Pathology at *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital from Iași, on 11 years (2007-2018) (*Costea et al., 2019*) (Figure 93).

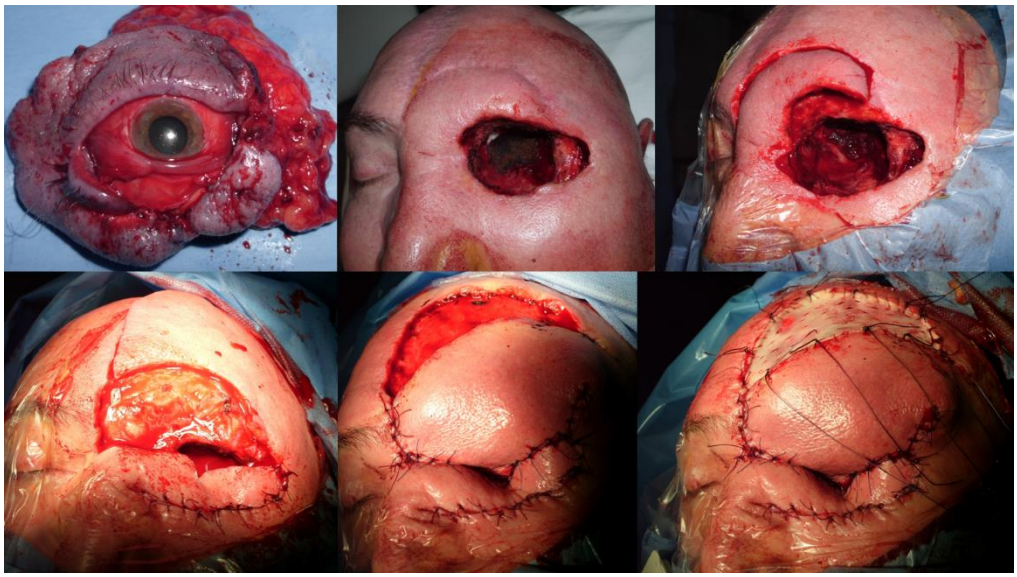

**Figure 93**. Intraoperative and postoperative images of a patient with periocular basal cell carcinoma and orbital extension (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*)

***Results and Discussions***

In the period 2007-2018, a total of 39 cases of periocular BCCs were diagnosed in our hospital between 2007 and 2018, and the characteristics of the patients and of the tumors are shown in the Table 31.

**Table 31**. The characteristic features of the periocular BCCs in our group (from *Costea et al., 2019*)

| Characteristics of the tumor | Frequency No. (%) |
|---|---|
| *Localization* | |
| ▪ Lower lid | 24 (61.5%) |
| ▪ Medial canthus | 7 (17.94%) |
| ▪ Upper lid | 5 (12.82%) |
| ▪ Lateral canthus | – |
| ▪ Unspecified | 3 (7.62%) |
| *Side* | |
| ▪ Right | 18 (46.2%) |
| ▪ Left | 21 (53.8%) |
| *Gross pathology* | |
| ▪ Vegetating lesion | 10 (25.64%) |
| ▪ Nodulo-ulcerative (rodent ulcer) | 29 (74.35%) |
| *Histological subtype* | |
| ▪ Nodular | 26 (66.7%) |
| ▪ With squamous differentiation | 8 (20.5%) |
| ▪ Adenoid | 4 (10.3%) |
| ▪ Morpheaform | 1 (2.6%) |

The mean age of the patients was 66 years (range 26-87 years), whereas the mean age reported in literature is 68 years (*Wu et al., 2014*). 56.4% (*n = 22*) of all the patients were women, with a female: male ratio of 1.78. Most patients (33.33%) were aged 70 to 79, and the most common histological subtype was the nodular one, representing 66.7% (*n = 26*) of all cases (Figure 94, 95, 96 and 97).

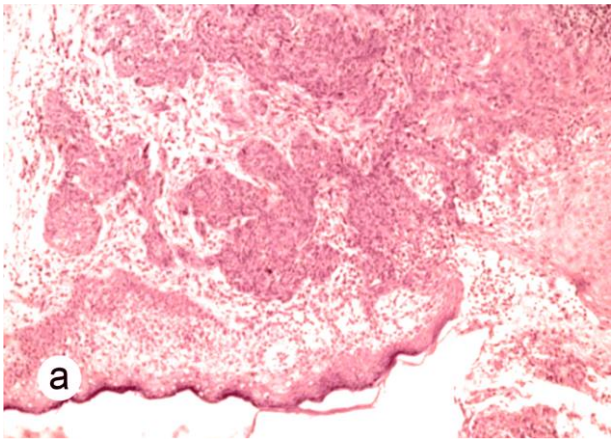


**Figure 94**. Nodular periocular BCC: The tumor maintained epidermal contact, but invaded the dermis (HE staining, x100). *Courtesy of Dr. G. F. Dumitrescu* (from *Costea et al., 2019*)

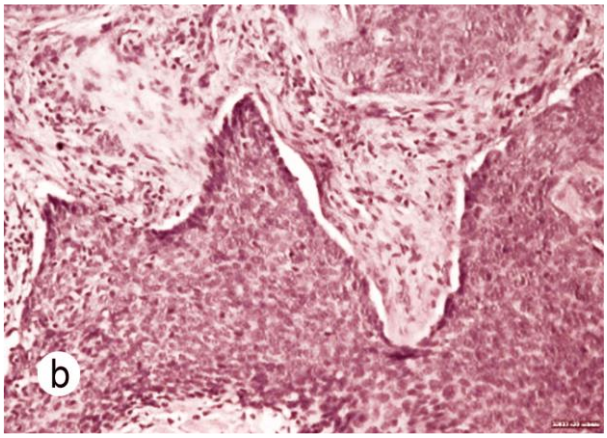


**Figure 95**. Nodular periocular BCC: Higher magnification of the same case revealed tumoral masses consisting of basaloid cells, with peripheral palisading and artefactual clefts (HE staining, x200) (from *Costea et al., 2019*)

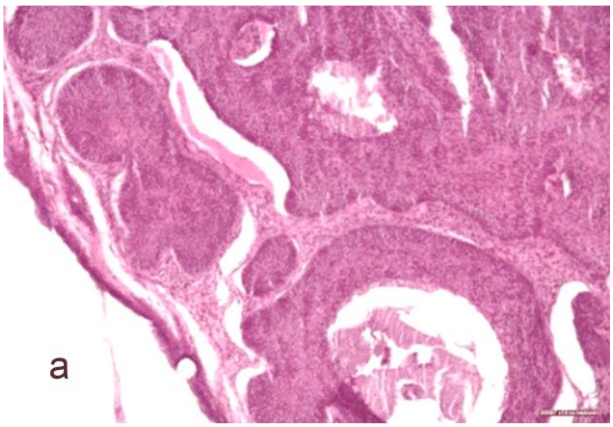


**Figure 96**. Nodular periocular BCC: Basophilic tumoral nodules infiltrated the dermis (HE staining, x100). *Courtesy of Dr. G. F. Dumitrescu* (from *Costea et al., 2019*)

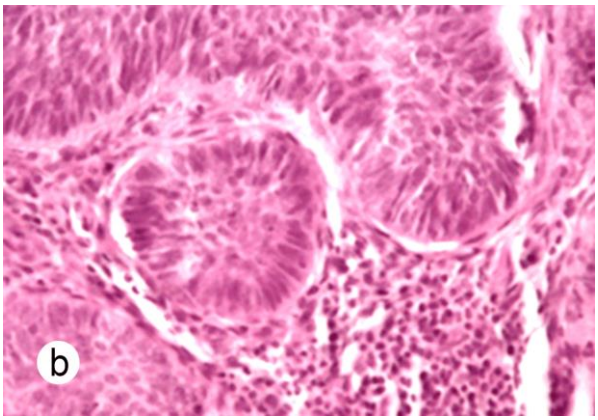


**Figure 97**. Nodular periocular BCC: The tumoral island presented a peripheral layer with a palisade arrangement, and was encircled by an artefactual retraction space between the tumor and the stroma – a strong chronic inflammation could be seen in the tumoral stroma (HE staining, x400). *Courtesy of Dr. G. F. Dumitrescu* (from *Costea et al., 2019*)

As regards eye localization, literature studies report lower eyelid as the most common localization of periocular BCC (52.7-63.1%) followed by the medial chantus (29.8%), upper eyelid (5.7-7.5%) and lateral chantus (*Lee, 1999a, Pornpanich and Chindasub, 2005, Spraul et al., 2000, Wu et al., 2014*), in agreement with our study (*Costea et al., 2019*).

When we correlated tumoral histological subtype with patient gender, we noticed that nodular periocular BCC occurs in basically equal rates in women and men. On the other hand, BCC with squamous differentiation and adenoid BCC occurred more commonly in women (Figure 98).

From the point of view of tumor localization at eye level, we noted that nodular periocular BCC predominantly occurs in the left eye (*n=14*), followed by BCC with squamous differentiation. Nodular BCC prevailed in the right eye (Figure 99).

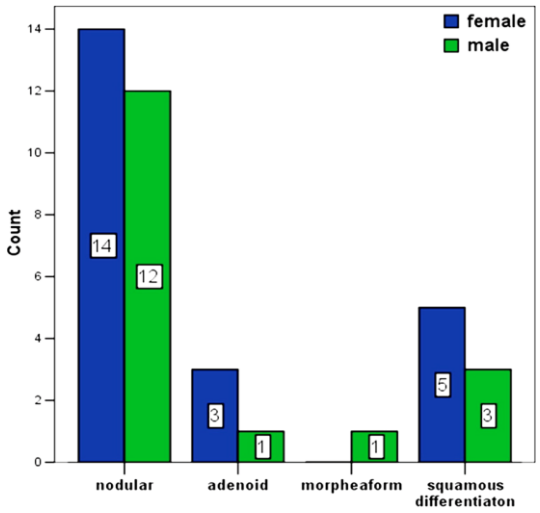


**Figure 98**. Distribution of periocular BCCs according to their histological subtypes (from *Costea et al., 2019*)

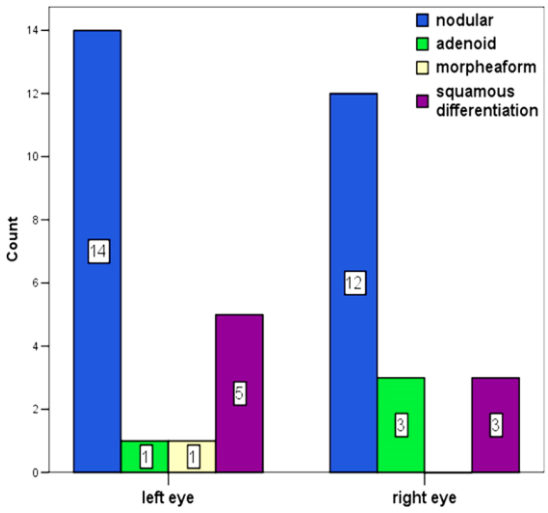


**Figure 99.** Periocular BCCs side localization according to their histological subtypes (from *Costea et al., 2019*)

According to our study, most periocular BCCs develop in older women, and their tumors are located in the lower eyelid, with a left-side preference. The immunohistochemical profile of periocular BCC we performed demonstrated strong immunopositivity for CK17 (Figure 100), suggesting that the origin of these cancers is in the follicular germinative cells.

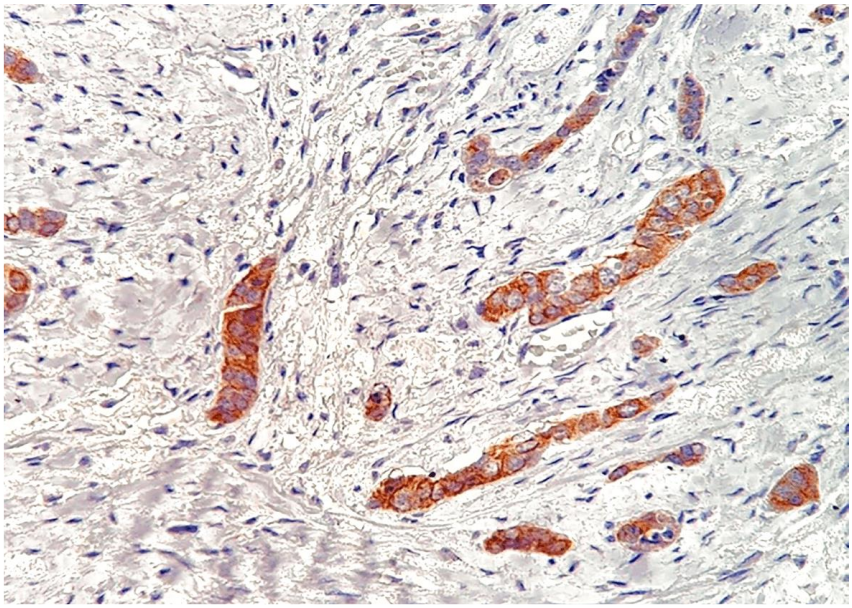

**Figure 100**. Periocular BCC with very intense CK17 expression (anti-CK17 antibody immunostaining, ×400).*Courtesy of Dr. G. F. Dumitrescu,* (from *Costea et al., 2019*)

Thus, we can consider that our findings appear to be representative for Central and Eastern European countries, probably due to the same genetic predispositions and environmental factors (*Costea et al., 2019*).

### I.4.4. Researches in neurosurgical anatomy and clinical neuroanatomy

*"We want perfect anatomical dissections, because we want perfect surgical operations"*
(Albert L. Rhoton Jr.) (*Matsushima et al., 2018*)

***Background***

Anatomy is the discipline that underlies neurosurgery, without which one cannot exercise this surgical specialty. Considered to be *the oldest child of mother medicine* (*Tubbs, 2014*), anatomy still has a major significance for neurosurgery, especially as anatomical research has evolved in recent years from methodological investigation to an educational and communication tool (*de Divitiis et al., 2019*).

In addition to visuospatial skills, the conceptual understanding of complex anatomy, which is a vital skill, is also extremely important in neurosurgical training (*Bernardo, 2017*). Thus, the development of a sense of the neuroanatomic relationship between vascular and neuronal structures encased by bone is extremely important and requires practice (*Kin et al., 2012*).

Among all the neuroanatomy branches, skull base surgery is one of the most demanding surgeries (*Scholz et al., 2010*) with major importance in neurosurgery practice, especially since in the last years minimally invasive neurosurgery has greatly progressed and the required anatomic knowledge for adequate surgery has increased (*de Notaris et al., 2014*).

### I.4.4.1. Surgical skull base anatomy with neurosurgical implications

*In the area of integrating clinical neuroanatomy with neurosurgical anatomy, I have published 3 reviews and 1 case report in a journal indexed in ISI Web of Science (1 paper) and in international databases (3 papers). The summary of the most important data is to be found hereunder:*

**Turliuc DM**, Sava A, Cucu AI, Turliuc S, Dumitrescu AM, Costea CF. *Cribriform plate and Galen's cribrum romanum.* Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology 2016, 15(1):123-126.

*This paper has 1 citation.*

**Turliuc DM**, Cucu AI, Costea CF. *3 years long-term posttraumatic cerebrospinal fluid fistula complicated with recurrent meningitis*. Romanian Journal of Oral Rehabilitation 2016, 8(4):95-99.

Costea C, Turliuc S, Cucu A, Dumitrescu G, Carauleanu A, Buzduga C, Sava A, Costache I, **Turliuc D**. *The „polymorphous" history of a polymorphous skull bone: the sphenoid. Anatomical Science International* 2018, 93(1):14-22. (Impact Factor in 2018 = 1.566)

*This paper has 2 ISI citations.*

**Turliuc D**, Trandafir D, Cucu A, Dobrin N, Dumitrescu G, Sava A, Dumitrescu AM, Costea CF. *Giant nasopharingeal carcinoma – a case report. Dynamic anatomical models in skull base and intracranial space invasion*. Romanian Journal of Oral Rehabilitation 2016, 8(1):51-58.

***Importance of knowing anterior skull base anatomy in neurosurgery***

Knowing the anatomy of the anterior cranial base is vital for skull base surgery, especially in tumor pathology, more particularly olfactory groove meningiomas, sphenoid jugum meningiomas or nasopharyngeal carcinomas with intracranial involvement. The term *cribriform plate* comes from the Latin words *cribrum* = sieve and *forma* = figure, and in neuroanatomy the term *cribriform plate* (*lamina cribrosa*) was used to describe the horizontal portion of the ethmoid bone (*Palmer, 1845*), which resembles a sieve crossed by the olfactory nerves to access the nasal cavity from the olfactory bulbs (*Robinson, 1918, Tingerides et al., 2013*) (Figure 101).

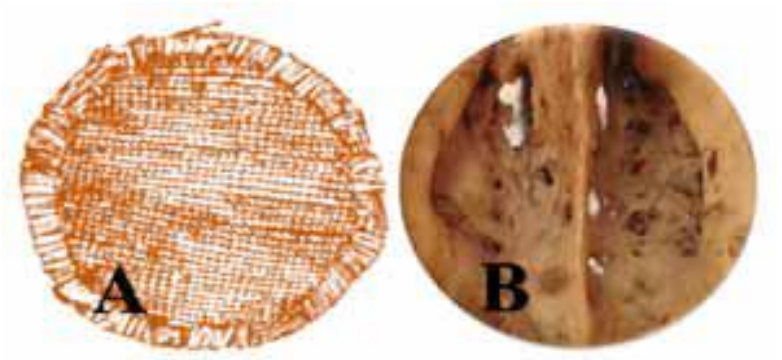


**Figure 101**. Cribrum romanum (adapted after *White, 1974*) (A). Cribriform plate of the ethmoid mode (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*) (B). (from *Turliuc et al., 2016c*)

The term *cribriform plate* was first used by Hippocrates (460-370 BC), who described this bone like a cartilage, soft like a sponge, but which is neither a bone structure, nor a flesh one and which he thought played a role in the sense of smell (*Turliuc et al., 2016c, Wright, 1902*). Although ancient anatomists believed that the cribriform plate was a self-standing bone separated from the ethmoid bone (*Turliuc et al., 2016c*), it was not until the 16th century that Gabriel Fallopius (1523-1562) brought the anatomic truth to light and corrected this error (*Macchi et al., 2014*), being the first anatomist to accurately describe the ethmoid bone, arguing that the cribriform plate is not a separate ossicle, but an integral structure of the ethmoid bone (*Turliuc et al., 2016c*).

The Sicilian physician Giovanni Filippo Ingrassias (1510-1580) subsequently described the true configuration of the ethmoid bone and was the first to observe and to delineate the anterior ethmoid cells (*Draf et al., 2015*). Ingrassias also depicted the other ethmoid bone structures, namely the crista galli, cribriform plate and perpendicular plate (*Cappello et al., 2010),* as well as the smaller wing of the sphenoid which he called processes of Ingrassias (*Kemper, 1905*).

Although the ethmoid bone is located in a difficult position to access and has a complicated form, the ethmoid bone and its cribriform plate have a long history filled with errors, which took centuries to correct, namely in the early 16th century (*Turliuc et al., 2016c*). The anatomists' contributions to cribriform bone anatomy have undoubtedly supported the development of knowledge and skull base surgery.

A rare case with traumatic involvement of the cribriform plate, in which we discussed the importance of clinical and surgical neuroanatomy in neurosurgery, was that of a 9-year-old female patient with a penetrating head trauma and 3 years long-term posttraumatic CSF leak complicated with recurrent meningitis (*Turliuc et al., 2016b*) (Figure 102).

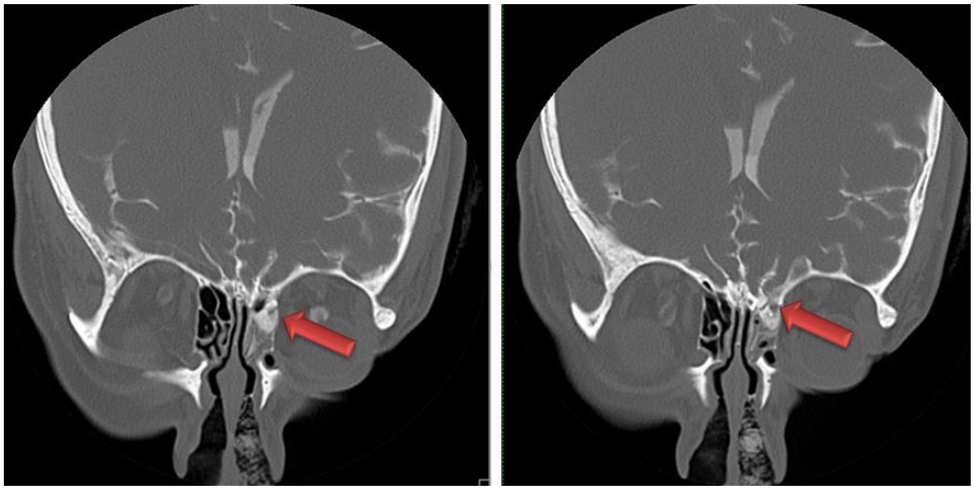

**Figure 102**. "CT cisternography: it reveals the contrast agent leaking from the subdural area to the right nasal fossa (red arrows)" (from *Turliuc et al. 2016b*)

Posttraumatic cerebrospinal fluid fistula occurs in 10-30% of the patients with cranial base fractures (*Loew, 1984, Marentette and Valentino 1991, Yilmazlar, 2006*) and in most cases it is diagnosed within the first 48 hours after injury. However, in our case, the patient was diagnosed with cerebrospinal fluid leakage after 3 years. This rare case is that of a patient with frontal comminuted fracture (sleigh accident) suffered at the age of 11 (in 2007) and with the occurrence of a posttraumatic CSF leak 8 years later, and complicated in the last 3 years with recurrent meningitis (between 2013 and 2015). Surgery was performed to close the CSF leak and the dural defect was corrected by covering the fracture line that passed through the right paramedian ethmoid bone (*Turliuc et al., 2016b*).

To conclude, since cerebrospinal leak occurring late after head injury may have a high rate of mortality and morbidity, early diagnosis is very important.

***Importance of knowing middle skull base anatomy in neurosurgery***

In neurosurgery, lesions of the skull base are a challenge, which is why good knowledge of the anatomy of the skull base is important. In this regard, I would like to mention a review of the anatomy of the sphenoid bone (*Costea et al., 2018*).

The paper includes a description of the anatomists' efforts to describe the sphenoid bone (Figure 103), to name its components and to achieve understanding of sphenoid conformation from Antiquity to its conception as a bone in the 18$^{th}$ century in modern Italy or France (*Costea et al., 2018*).

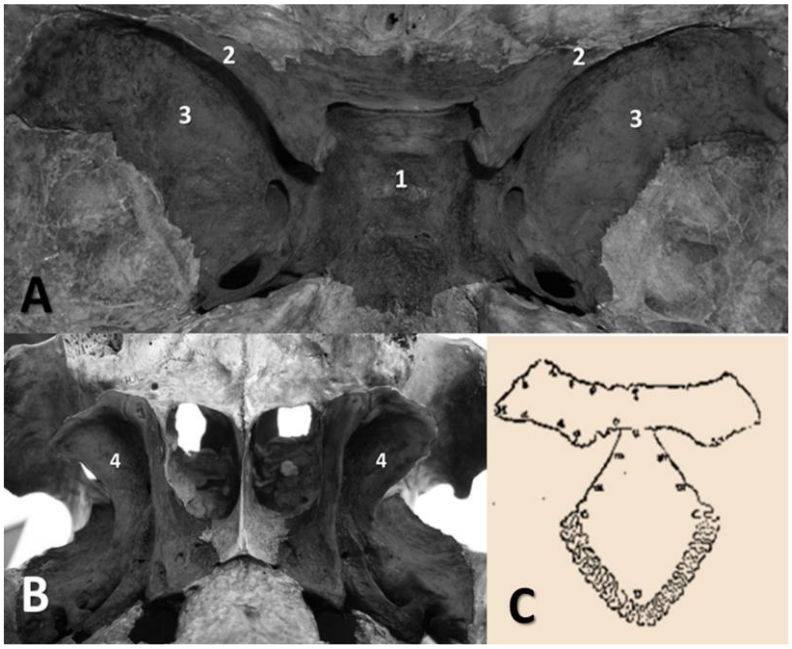


**Figure 103**. "Endocranial view of the sphenoid bone (A). Exocranial view of the sphenoid bone with the pterygoid plates (B). Vesalius's drawing of the sphenoid bone (adapted from *De Humani Corporis Fabrica*, 1555) (C)" (from *Costea et al., 2018*)

By naming the anatomic structures by similarity and by utilizing the analogies between the shapes of new structures and those around, we have achieved a *historical construction* of each anatomical term (*Arráez-Aybar et al., 2015, Costea et al., 2018*) (Figure 104).

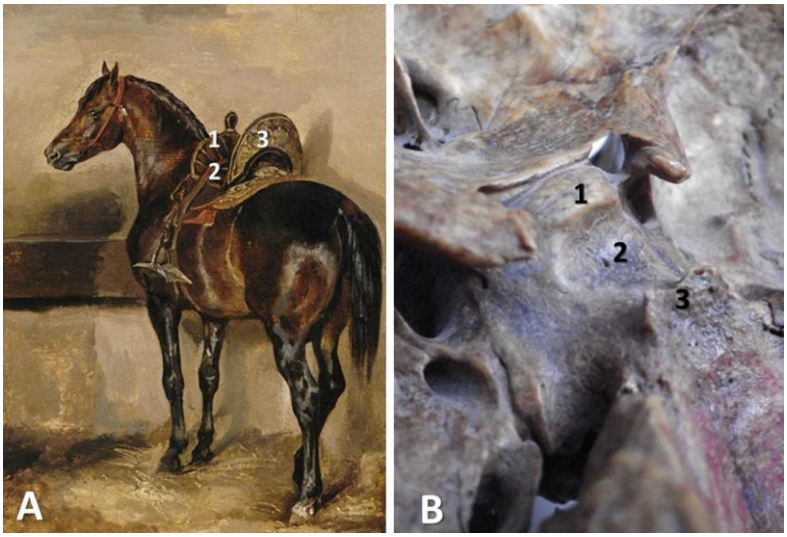


**Figure 104**. "Turkish Horse in a Stable by Theodore Gericault (1791–1824) (public domain) (A). The anatomy of the sella turcica: tuberculum sellae (1), hypophysial fossa (2), and dorsum sellae (3) (B)" (from *Costea et al., 2018*)

Thus, increasing the notions of anatomy of cranial base promoted the bringing to light of skull base surgery (*Prestigiacomo and Dagi, 2012*). The deep localization of the sphenoid bone in the skull base made it difficult for anatomists to understand its anatomy. Therefore, the history of its

comprehension is recent and complicated (*Costea et al., 2018*).

Knowing the anatomy of the cranial base has led to the understanding of various tumoral and non-tumoral neurosurgical pathologies. Thus, starting from the case of a patient with giant nasopharyngeal carcinoma (NC) extending in all three skull base fossae, we tried to explain a few anatomical models of the skull base and also intracranial space invasion (*Turliuc et al., 2016d*) (Figure 105).

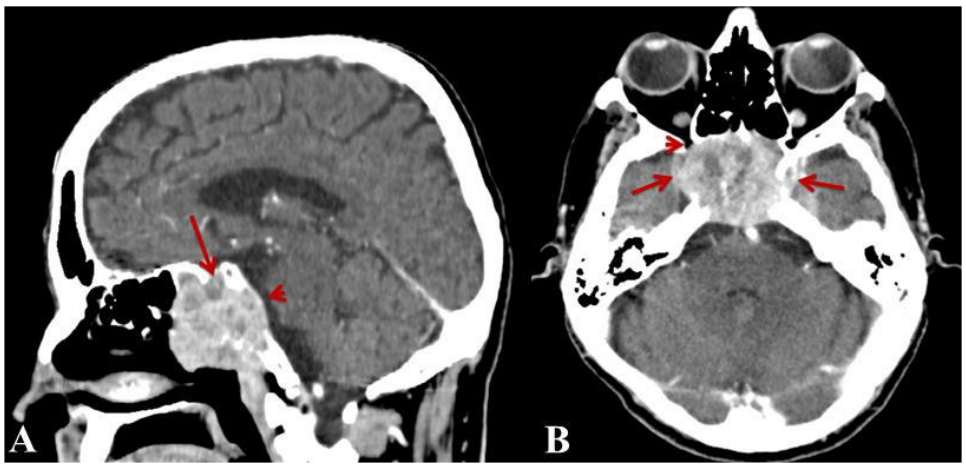


**Figure 105**. Head contrast-enhanced CT scan (sagittal image) where sella turcica (red arrow) and clivus (red arrow head) are observed (A). Axial contrast-enhanced CT scan where the right orbital apex invasion (red arrow head) and bilateral cavernous sinus invasion (red arrows) are observed (B) (from *Turliuc et al., 2016d*)

Skull base invasion by the tumor occurs in 25-65% of the cases of NC and it is one of the poorest prognostic factors (*King et al., 1999, Roh et al., 2004, Li et al., 2013*). The tumor may extend into the skull base through all three skull base fossae (anterior, middle and posterior cranial fossa), using the numerous foramina and fissures in the skull base, through which the NC may expand to the intracranial space. Of all these three fossae, the NC most frequently expands into the middle cranial fossa, as it is closest to the nasopharynx (*Turliuc et al., 2016d*) (Figure 106).

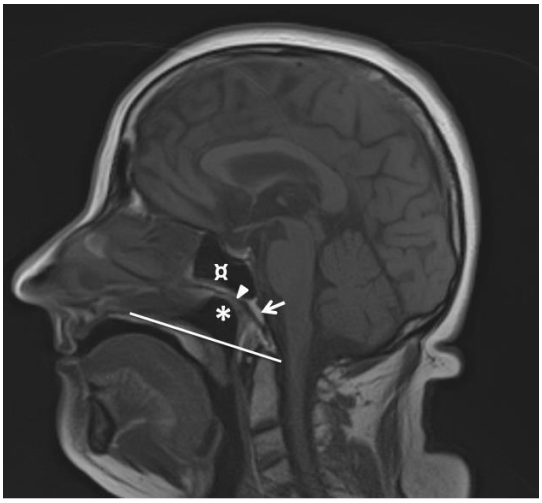

**Figure 106**. Sagittal T1- weighted MRI image showing the normal nasopharynx (asterisk) and its upper limit represented by the basiphenoid (arrow head) and clivus (arrow). Above, the sphenoid

body with a large sphenoid sinus (¤). Below, the junction between nasopharynx and oropharynx (white line) is represented by a line between the hard palate and anterior arch of C1 vertebra (from *Turliuc et al., 2016d*).

Several models of skull invasion have been suggested in literature, in an attempt to support surgeons and radiologists both in NC therapy, and in its early detection, although no consensus has yet been reached in this respect. From this point of view, van Huijer divided the lateral skull base in 6 invaded anatomic regions: (1) *nasopharyngeal region*, (2) *oropharyngeal region*, (3) *acoustic region*, (4) *neurovascular region*, (5) *articular region* and (6) *infratemporal region* (*Han et al., 2012, Wang and Mao, 2001, Wu, 2007*).

As concerns this invasion model, Han *et al*. reported that NC invaded the nasopharyngeal region in 100% of the cases, followed by the oropharyngeal region in ~74% of the cases, the neurovascular region in ~ 49% of the cases, the infratemporal region in ~ 42% of the cases, the acoustic region in ~ 25% of the cases and the joint region in ~ 9% of the cases (*Han et al., 2012*). The oropharyngeal region ranks second in this classification due to the fact that after it has invaded the region of nasopharynx, NC ascends through the natural anatomical orifices existing at this level, such as the Eustachian tube, located bilaterally on the nasopharynx walls, and which is projected posterolaterally to the skull base (*Turliuc et al., 2016d*).

As regards skull base erosion, the most commonly involved is the sphenoid body, followed by the clivus, pterygoid plates and petrous apex, and one explanation for the predilection for these bone structures is that these anatomical sites are very close to the tumor and have no tissue barrier (*Li et al., 2013, Liu et al., 2009*). In the order of bone invasion frequency, these localizations are followed by the greater wing of the sphenoid bone, foramen lacerum, lateral pterygoid process, foramen magnum and cavernous sinus. In the final stages, the tumor may even extend to the ethmoid sinus, jugular foramen, occipital condyle, foramen ovale, or lateral plate of atlas (*Li et al., 2013, Turliuc et al., 2016d*).

As far as tumor invasion of various regions of the skull base is concerned, in a study by Han *et al.* the cavernous sinus and internal carotid canal were reported as the most common localizations, followed by the sphenoid sinus, clivus and sella turcica. In the same study, the authors reported that tumor invasion of the cranial base depends on the place of origin of the tumor at nasopharynx level (*Han et al., 2012*).

In conclusion, there is no consensus between the pathological anatomy models of skull base and intracranial space invasion by NC suggested in literature by various authors. Nonetheless, we may consider that NC may invade the skull and intracranial space through all the anatomical orifices, along the vessels or nerves, as well as through the bone destruction areas caused by the tumor.

The rarity of the case reported by us consisted of the fact that the patient's clinical symptomatology was poor compared to the giant tumor size and that the tumor had invaded the anterior, middle and posterior fossae of the cranial base (*Turliuc et al., 2016d*).

### I.4.4.2. Research on brain anatomy and neurosurgical neuroanatomy

***Background***

The anatomy of the human body is one of the most ancient branches of medicine and it may be considered one of the elemental pillars of medical education (*McLachlan and Patten, 2006*). Nowadays, the technical advances in the new branches of medicine have cannibalized anatomy and reduced its relevance (*Arráez-Aybar et al., 2010*).

Moreover, over the last two centuries, neurological dissections for learning neuroanatomy have switched focus from the study of the anatomy to promoting the understanding of neurophysiology, neuropathology and techniques used in neurosurgery (*Aboud et al., 2002, Cappabianca and Magro, 2009, Moon et al., 2010*). Nevertheless, neurosurgical cadaveric training is still a *sine qua non* requirement for both learning and practicing neurosurgery, as well as for developing one's technical skills before passing to living patients.

This is precisely why anatomy is often approached rather as a task for rote memorization than for conceptual understanding (*Bernardo, 2017*). Regarding the brain anatomy, attempts have been made to find an analogy between the names of certain anatomic terms which are frequently used in neurosurgery and the shape, localization and function of the anatomic structures that they denominate. All the more so as knowledge about the origin of anatomical terms is currently extremely helpful for better understanding anatomical structures (*Paluzzi et al., 2012*).

*With a view to the conceptual understanding of some neuroanatomical terms and structures frequently used in neurosurgery, we have conducted three studies, together with my collaborators of the Department of Neurosurgery and Department of Pathology at Prof. Dr. Nicolae Oblu Clinical Emergency Hospital, and also in several departments of Grigore T. Popa University of Medicine and Pharmacy. They were published in 3 review articles in journals indexed in ISI Web of Science, and the summary of the most important data included in these studies is as below:*

**Turliuc DM**, Turliuc S, Cucu AI, Sava A, Dumitrescu GF, Carauleanu A, Buzduga C, Trandafir D, Costea CF. *An unwritten anatomy lesson: the influence of Roman clothing on neuroanatomical terminology: in memoriam Albert L. Rhoton, Jr. (1932–2016*). Clinical Anatomy 2016, 29:680-690. (Impact Factor in 2016 = 1.824)

**Turliuc D**, Turliuc S, Cucu A, Dumitrescu GF, Carauleanu A, Buzduga C, Tamas C, Sava A, Costea CF. *A review of analogies between some neuroanatomical terms and Roman household objects*. Annals of Anatomy 2016, 204:127-133. (Impact Factor in 2016 = 1.864)

*This paper has 1 ISI citation.*

**Turliuc D**, Turliuc S, Cucu A, Dumitrescu G, Costea C. *An entire universe of the Roman world's architecture found in the human skull*. Journal of History of the Neurosciences 2017, 26(1):88-100. (Impact Factor in 2017 = 0.288 )

*This paper has 2 ISI citations and a total of 4 citations.*

***Fimbriae hippocampi***

In Ancient Rome, married women (called *matrons*) wore around their neck a necklace called *segmentum*, which looked like a tape decorated with fringes, called *fimbriae* (*Adam et al., 1842*). They were also found in other pieces of clothing for women (Figure 107). Whereas Herophilus, Eudemus and Rufus initially described the fringes of the fallopian tubes (*Buck and Stedman, 1914*), Gabrielle Fallopius (1523-1562) was the one who introduced the term *fimbriae* in the anatomical terminology (*Herrlinger and Feiner, 1964*).

In neuroanatomy, the term *fimbriae hippocampi* was described much later by the great anatomist Andreas Vesalius (1514-1564), although he was not the one who gave it its current name (*Catani and Sandrone, 2015, Finger, 1994, Swanson, 2014*). Vesalius succeeded this performance, after Costanzo Varolio (1543-1575) had implemented a new brain dissection method (*French, 1999, Martensen, 2004*).

The anatomist Raymond de Vieussens (1635-1715) was the one who called it fimbria of the hippocampus (Figure 108), excited by its resemblance to fringed clothing, after he had reintroduced nerve fiber dissection according to the method of the anatomist Thomas Willis (1621-1675). Vieussens was the one who called it *fimbriae fornicis* (*Vieussens, 1685*).

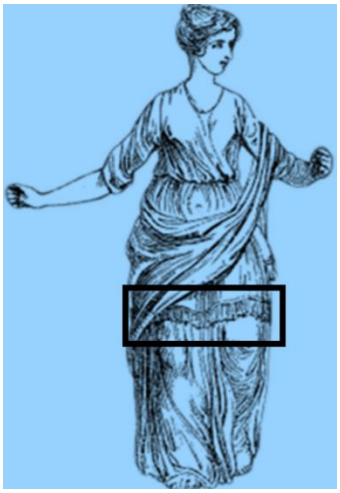

**Figure 107**. Roman clothing with *fimbriae*. (public domain)

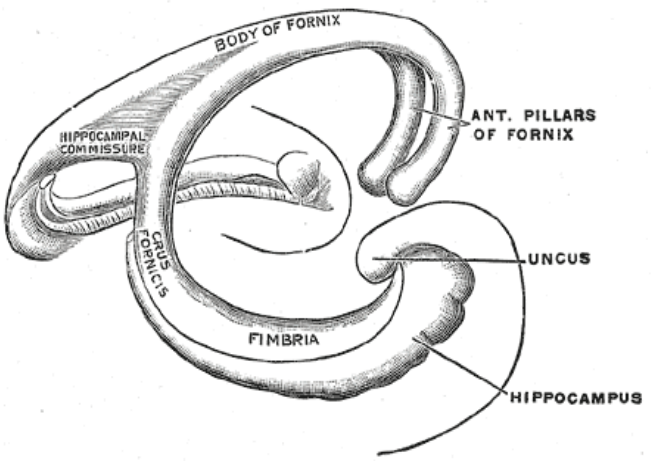


**Figure 108**. Shape of human hippocampus and associated structures (from *Gray, 1918*). (public domain)

***Velum interpositum***

In anatomical terminology, *velum interpositum* is a "triangular space between two layers of the tela choroidea from the third ventricle" (*Rhoton, 2002, Turliuc et al., 2016e*) (Figure 109). The first who recommended the use of *velum interpositum* in neuroanatomy was Albrecht von Haller (1708-1777) (*Turliuc et al., 2016e).* He was also the one who distinguish between velum and choroid plexus, which were two anatomical structures which most anatomists before him had confused (*Swanson, 2014*). Haler's initial name was *veli sive plexus choroideis interpositi* (*Swanson, 2014*), and the anatomist got inspired by the Roman veil (*velum)* (*Cleland, 2007, Smith, 1853*) (Figure 109). The anatomist Charles Bell (1774-1842) later named *vellum interpositum* also velum of Haller (*Bell, 1802*).


**Figure 109.** Velum interpositum (from *Gray, 1918*) (A). Image of Roman velum from *Ara Pacis Augustae* (*Altar of Augustan Peace*), 'Tellus' panel – detail (B). (public domain)

***Funiculus***

Ancient Romans used the *funiculus* (diminutive from *funis*) as a clothing accessory. This was nothing else than a cord utilized to fix clothing (*Johnson, 1827, White, 1975, Smith and Anthon, 1843*) (Figure 110). Once the distinction between gray and white substance of the spinal cord was made in 1572 (*Schmahmann and Pandya, 2009*), later, in 1666, the anatomist Gerard Leendertszoon Blasius (1627-1682) managed to illustrate the dorsal and lateral funiculus, without naming these structures in any way (*Swanson, 2014*).

The term *funiculus* was only later introduced in neuroanatomy (Figure 110), more precisely in 1822, by the brilliant Karl Friedrich Burdach, who described the structuring of the white matter of spinal cord, referred to the anterior, lateral and posterior funiculus (*Burdach, 1822*).

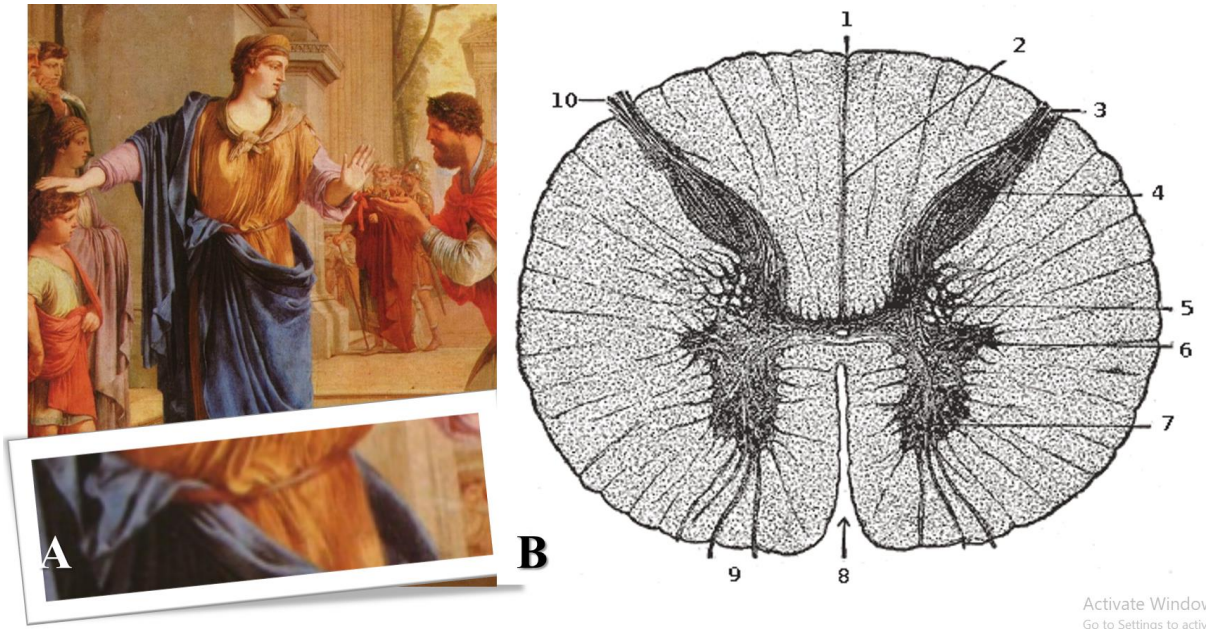


**Figure 110**. Cornelia rejecting the crown of the Ptolemies - detail (1646), *by Lauren de La Hyre (1606-1656), Museum of Fine Arts, Budapest* (A). Cross section of the spinal cord: (1) posterior median sulcus, (2) posterior median septum, (3) postero-lateral sulcus, (4) posterior column, (5) formatio reticularis, (6) lateral column, (7) anterior column, (8) anterior median fissure, (9) anterior nerve roots, (10) posterior nerve roots (from *Gray, 1918*) (B). (public domain)

***Cingulate gyrus***

Another piece of clothing in Ancient Rome that inspired anatomists was the *cingulum* (Figure 111), which was a waist belt worn either by priests or military (*cingulum militare*), or by women (*Friedman and Osberg, 1977, Lebby, 2013*).

In neuroanatomy, *cingulum* is a gyrus comparable to a girdle (Figure 111). Initially described in 1809 by the genius Johann Christian Reil, that called it *tenia tecta*, it was later named *cingulum* (Die Zwingen = *cingula*), as it resembled the Roman belt, in 1822, by Karl Friedrich Burdach (*Burdach, 1822*).

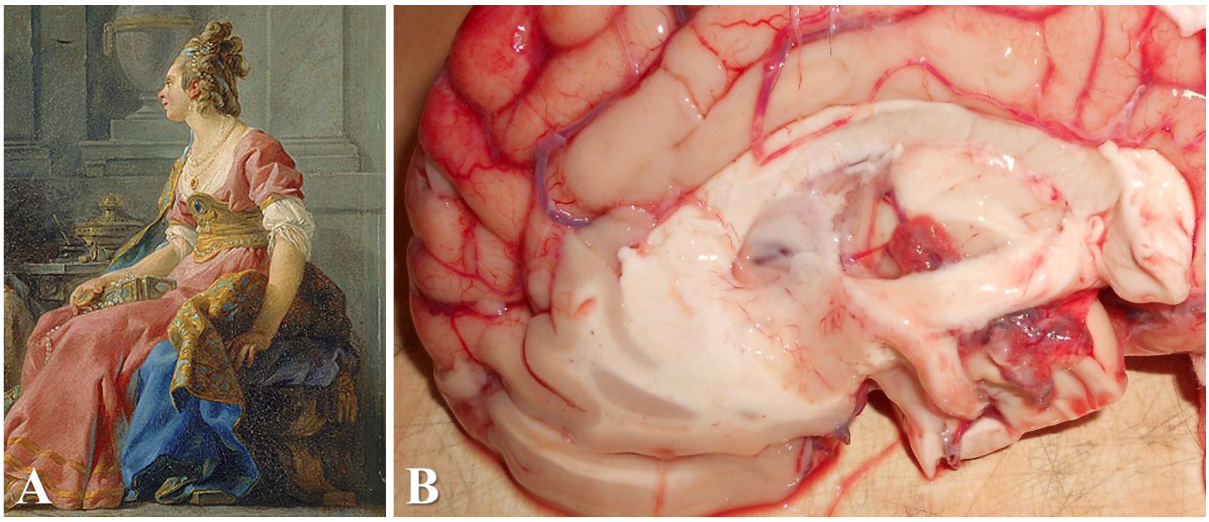


**Figure 111**. Cornelia Africana, Mother of the Gracchi - detail (1779), *by Nöel Hallé (1711-1781), Fabre Museum, Montpellier* (public domain) (A). Cingulate gyrus surrounding most of the corpus callosum like a belt. *Courtesy of Dr. G. F. Dumitrescu* (B)

***Medial and lateral lemniscus***

Romans also wore the *lemniscus* (Lat *lemniscus* = band), a band used like a head ornament (*Smith and Anthon, 1857*) or attached to crowns, hanging down to the back of the neck (*Smith, 1853, Smith and Anthon, 1857*) (Figure 112).

In anatomical terminology, Johann Reil was the one who introduced the term *lemniscus* in 1809 to characterize the course of a white matter band through the pons and mesencephalon (*Turliuc et al., 2016e*). Louis Gratiolet (1815-1865), a modern French anatomist, later named this structure *le ruban de Reil*, in Reil's memory (*Hyrtl, 1880*).

With the development of neurosciences in the 19$^{th}$ century, the neuropathologist Theodor Hermann Meynert (1833-1892) distinguished the two parts of the lemniscus: medial or superior and lateral or inferior (*Meyer, 1971*), also suggesting that superior lemniscus would be a sensory tract (*Boivie, 1971*).


**Figure 112**. "The brainstem (lateral view) with medial lemniscus (blue) and lateral lemniscus (yellow) (from *Gray, 1918*) (A). The Augustus Emperor cameo located in the centre of The Cross of Lothair revealing the lemniscus over the neck (*Aachen Cathedral Treasury, early first century*) (B). Romanian Byzantine iconography represented an angel with lemniscus (C)". (public domain) (from *Turliuc et al., 2016e*)

***Corona radiata***

Also in Ancient Rome, the crown was a circular adornment, usually realized of metal alloys and decorated with flowers and leaves. The crowns were offered as a reward for a military success, a special talent, a victory or a civil merit (*Turliuc et al., 2016e)*. Among these types of crowns, the Corona Radiata was offered to either worshiped heroes or gods, and sometimes it was worn by the emperor as a sign of his divine nature (*Smith, 1853*) (Figure 113).

In neuroanatomy, the term *corona radiata* was used by the anatomist J.C. Reil to characterize the radiation of white matter tracts from the depths of the brain (*Reil, 1812, Turliuc et al., 2016e*) (Figure 113).

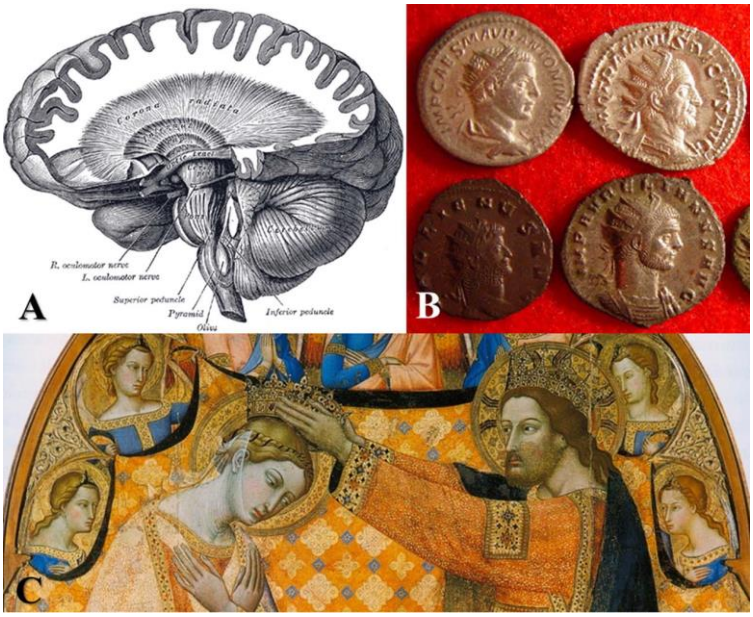

**Figure 113**. "Corona radiata (from *Gray, 1918*) (A). Coins from Ancient Roman period, representing Roman Emperors with radiate crowns (B). God crowning Virgin Mary as Queen of Heaven (*Jacopo di Mino del Pellicciaio, Coronation of Virgin-detail, 1340-1350*) (C)". (public domain) (from *Turliuc et al., 2016e*)

***Pulvinar, the largest nucleus in the primate thalamus***

In ancient Rome, the pulvinar was an armchair, an *empty throne* in which Romans used to place their deities, especially during the *Lectisternium*, which was a celebration of their reconciliation with their gods (*Smith, 1859*).

In anatomical terminology, the term pulvinar describes the caudal nucleus of the thalamus (Figure 114), and the first to use this name was the anatomist Karl Friedrich Burdach (1776-1847) (*Turliuc et al., 2016f*).

Although Burdach did not know exactly the possible functions of the thalamus (or of the pulvinar), he accurately described its localization: *"Das Polster (pulvinar), eine Anschwellung am hintern Ende des inner Randes der obern Vierhügel wie ein Kissen herüber legt* [The cushion (pulvinar), a swelling at the posterior end of the inner edge of the upper quadrigemina like a pillow over seats (our translation)]" (*Burdach, 1822, Turliuc et al., 2016f*).

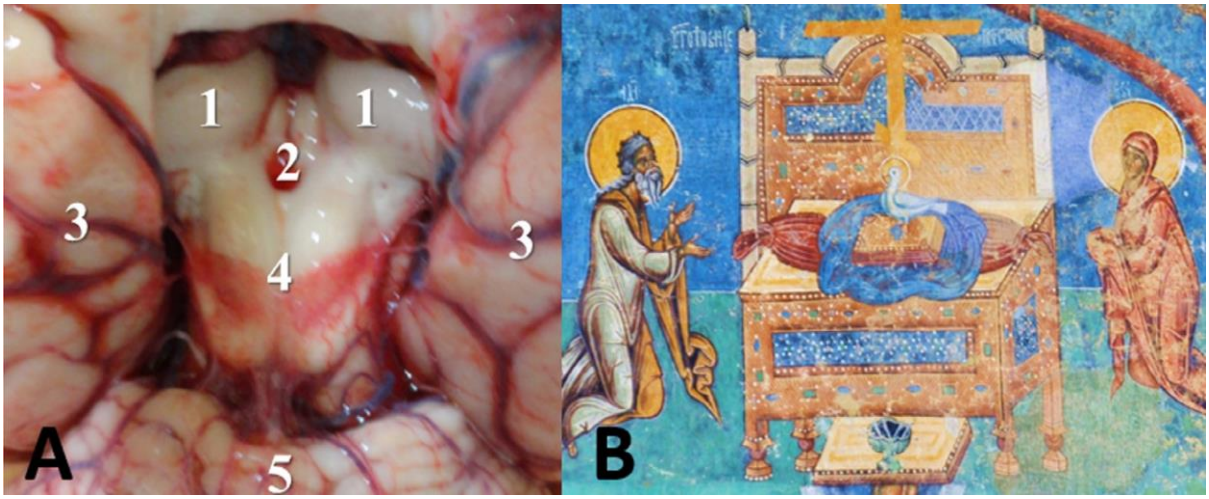


**Figure 114**. "Posterior view of the pineal region with: (1) pulvinar nuclei, (2) pineal gland, (3) medial view of occipital lobes, (4) tectal plate, (5) cerebellum (*Courtesy of Dr. G. F. Dumitrescu)* (A). Hetoimasia, equivalent of the Roman empty throne (pulvinar) (or Throne of the Second Coming of Christ), used in Byzantine iconography on exterior picture of the western wall of Voronet Monastery, Romania, 1535 (detail) (B)" (from *Turliuc et al., 2016f*)

***Internal external and extreme capsule***

In any Roman house, there was a *capsa* or *capsule*, a small cylindrical box where books were kept (*Diab, 1999, Turliuc et al., 2016f*) (Figure 115).

In neuroanatomy, the term *capsule* (Kapsel) was introduced in 1809 by Johann Christian Reil to refer to the structure that sourrounded basal ganglia as a recipient (*Reil, 1809a*) (Figure 115).

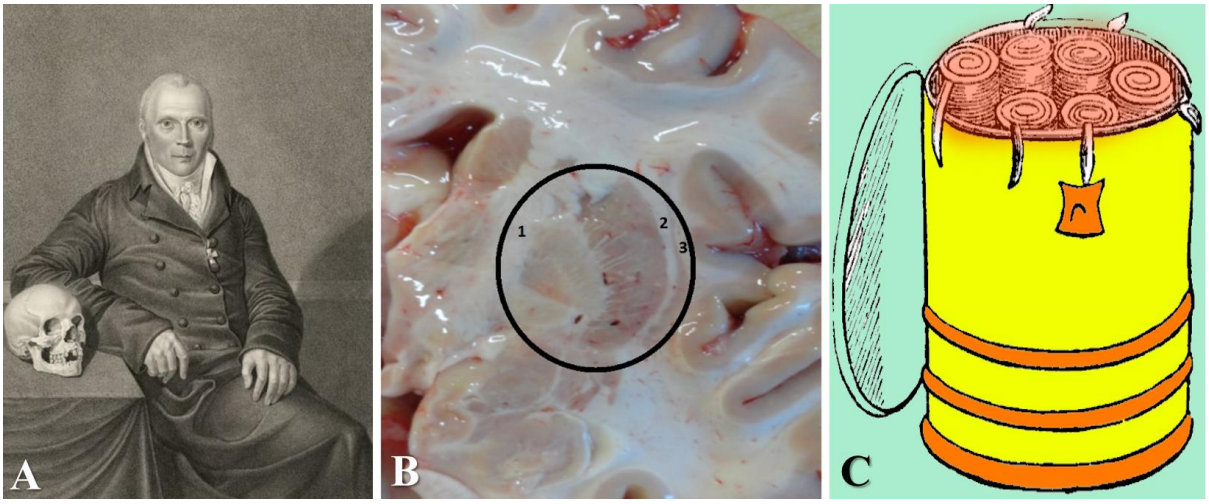


**Figure 115**. Johann Christian Reil (1759-1813) (portrait from 1811) (A). Coronal section of the brain showing: (1) internal capsule, (2) external capsule and (3) extreme capsule. *Courtesy of Dr. G. F. Dumitrescu* (from *Turliuc et al., 2016f*) (B). An open capsa with six rolls of books in it - from a painting at Pompeii (adapted from *Smith, 1859*) (C)

***Infundibulum***

The *infundibulum* (Figure 116), an object shaped like a funnel, was used in everyday life in Ancient Rome to pour liquids from one container to another. In neuroanatomy, the *infundibulum* was first described by the famous anatomist Rufus from Ephesus (80-150 AD) (*Diab, 1999*). Galenus of Pergamon (129-200 AD) and later Andreas Vesalius (1514-1564) also helped to the understanding of its anatomy.

Due to brand-new staining methods for the nervous tissue and to the use of microscope, the anatomist and pathologist J. Cruveilhier (1791-1874) managed to examine the brain and better describe the *infundibulum* in the 19th century. He also argued that this infundibulum is a funnel-shaped channel wider at the upper part, which communicates with the third ventricle (*Turliuc et al., 2016f*).

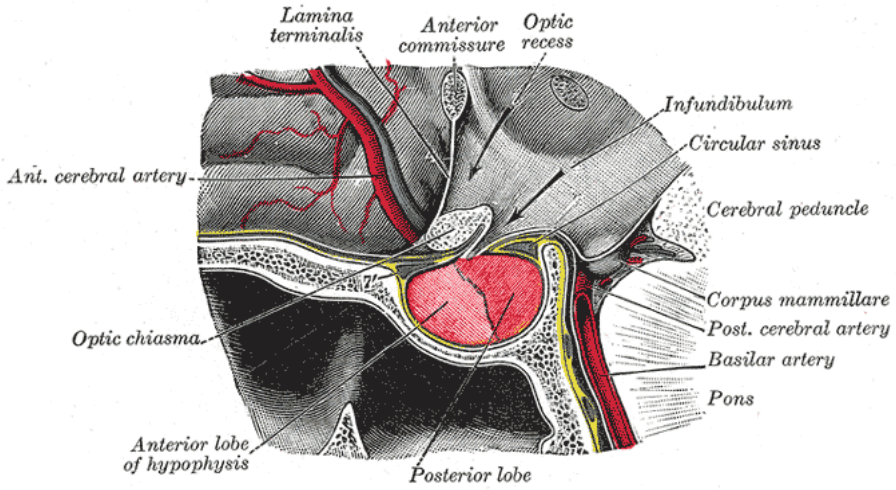


**Figure 116**. Sagittal section of the pituitary gland, showing the infundibulum (from *Gray, 1918*). (public domain)

***Operculum***

The *operculum* was another object used in Ancient Rome that inspired anatomists. It was a lid which served to cover food recipients (*White, 1975*).

The anatomist J.C. Reil was the first to describe the anatomical structure of the operculum (Figure 117), which he called *das Dach der Sylvischen Grube* (roof of the Sylvian pit) (*Reil, 1809b, Turliuc et al., 2016f*). Burdach later followed in Reil's footsteps and, in 1822, he utilized the word *der Klappdeckel* (flap cover) to refer to it, the equivalent of the Latin word *operculum* (*Burdach, 1822*) (Figure 118).

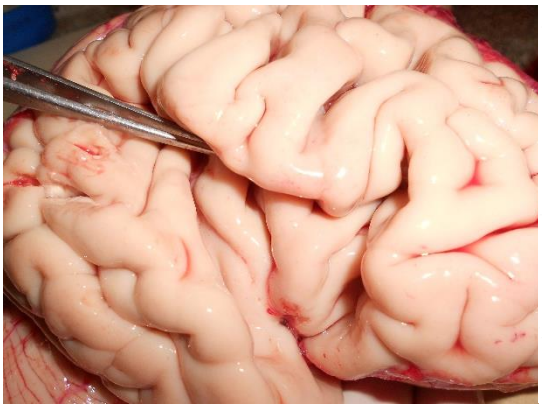

**Figure 117**. Lobe of insula with opercula (*Courtesy of Dr. G. F. Dumitrescu*)

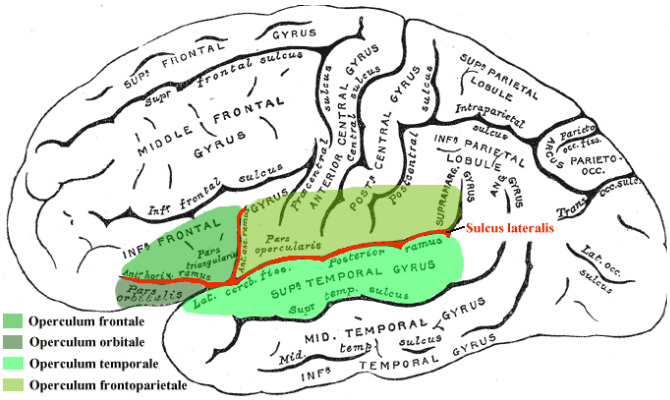


**Figure 118**. Opercula of the brain (adapted after *Gray, 1918).* (public domain)

***Flocculus cerebelli***

In Ancient Rome, the *flocculus* was a little tuft of wool (*Venes, 2013*) and inspired anatomists to appoint one of the cerebellum lobe (*Turliuc et al., 2016f*) (Figure 119).

Vincenzo Malacarne (1744-1816) (Figure 119) was the first to recognize this small cerebellar lobe, for which he coined the name *flossi laminose* (*Malacarne, 1776*), followed by Félix Vicq d'Azyr who called *flocculus* in the masterpiece *Traité d'Anatomie et de Physiologie* (*Meckel, 1838*).

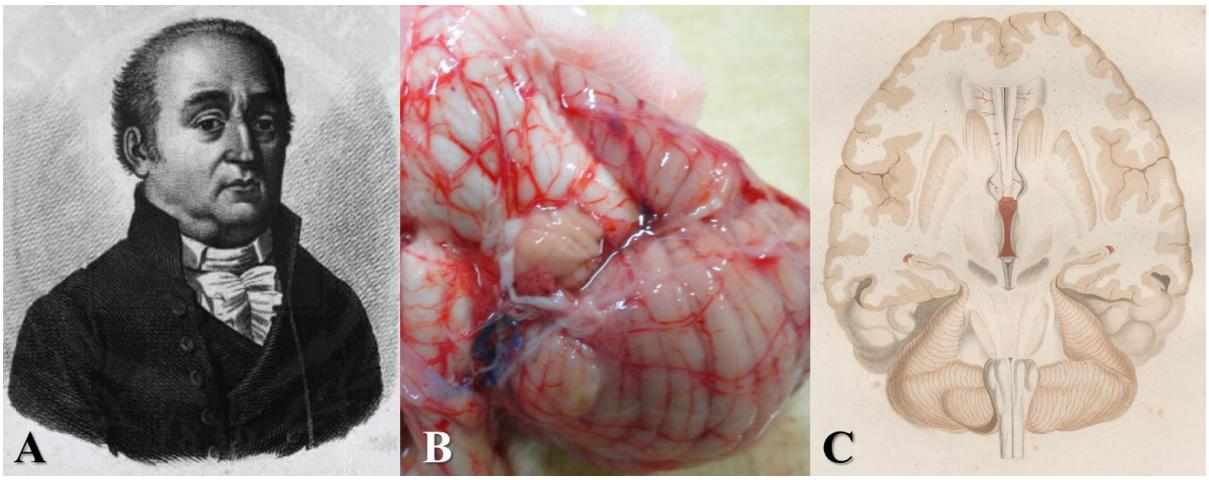


**Figure 119**. Vincenzo Malacarne (1744-1816) (public domain) (A). Macroscopic image with flocculus cerebelli (*Courtesy of Dr. G. F. Dumitrescu*) (B). *Traité d'Anatomie et de Physiologie, Félix Vicq d'Azyr (1786)* (C). (public domain)

***Forceps major and minor***

The Romans used an instrument called *forceps (Smith, 1859)* (Figure 120) to pull out the reddened iron from the fire. In neuroanatomy, the term is used in the form *forceps minor* and *forceps major* to describe white matter bundles that cross between the cerebral hemispheres (Figure 120), being thus described and named for the first time by the J.C. Reil, who called them *die Zange* (forceps) (*Reil, 1809c*).

A few years later, the anatomist Friedrich Arnold (1803-1890) calling these to structures *forceps minor* (anterior) and *forceps major* (posterior) (*Arnold, 1838*).

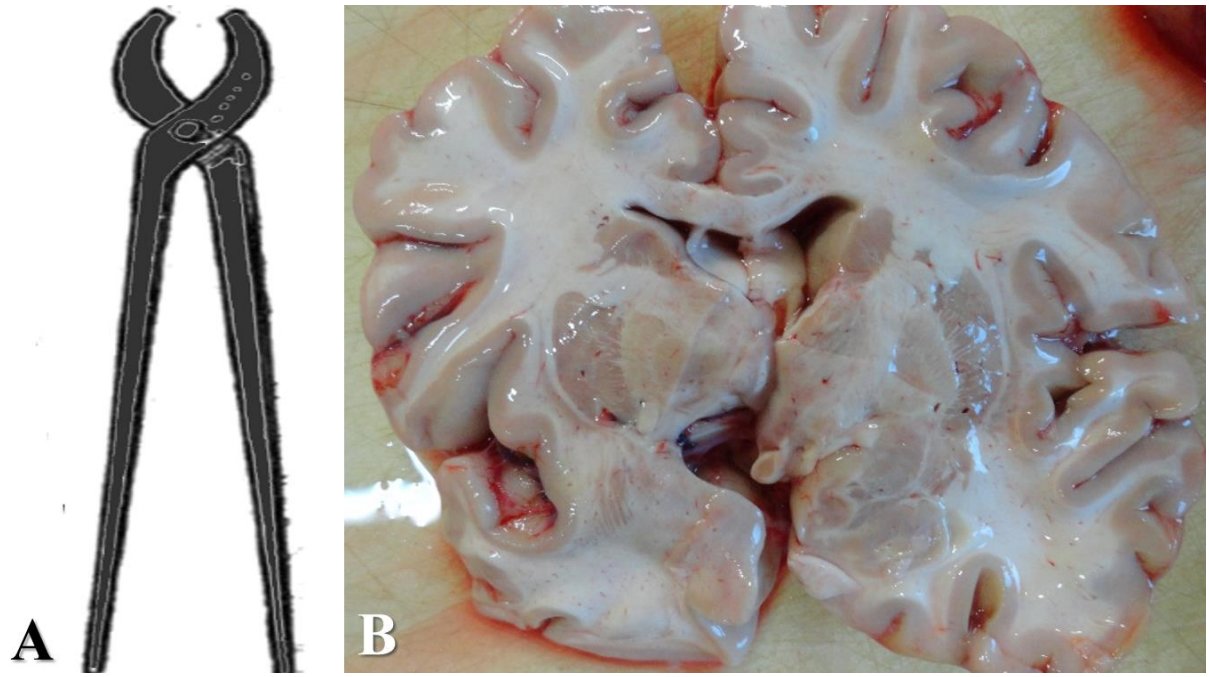


**Figure 120**. Roman instrument forceps (public domain) (A). Macroscopic anatomical image showing forceps minor (*Courtesy of Dr. G. F. Dumitrescu*) (B).

***Falx cerebri***

Roman peasants and farmers used a curved knife called *falx* (*Rich, 1860*). In neuroanatomy, the term defines a sickle-shaped fold of the duramater separating the cerebral hemispheres (Figure 121) and it was first represented in detail by Vesalius in his *Processes of the Hard Membrane* section (*Vesalius et al., 1543/2009, Turliuc et al., 2016f*).

The anatomist Albrecht von Haller (1708-1777) later called this anatomical structure falx: *"In universum, duo similes & æquales cerebelli lobi sunt, quos falx, a dura membrana encephali nata, haudprofunde bipartite' (von Haller, 1757–1766) [Generally speaking, the two cerebellar lobes are similar and equal, deeply divided by sickle (falx), a naturally hard membrane of the brain* (our translation)]" (*Turliuc et al., 2016f*).

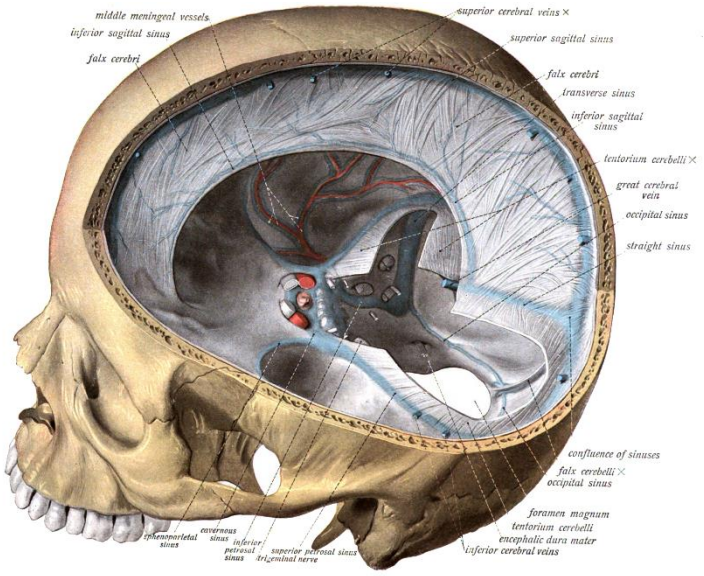


**Figure 121**. Falx cerebri in relation to the skull (from *Sobotta, 1908*) (public domain)

***Thalamus***

The Greek called their bedrooms thalamos and the Romans later turned this name into thalamus. Galenus initially named the third ventricle *thalamus*, convinced that is the inner chamber of the brain (*Turliuc et al. 2017a*).

Later, Andreas Vesalius drew thalamic nuclei with the basal nuclei and the internal capsule in *De Humani Corporis Fabrica* (*Vesalius, 1543*), achieving the first clear delimitation between the thalamus and the basal nuclei (*Parent, 2012*).

The first nuclear subdivision of the thalamus was later suggested by the physiologist Karl Friedrich Burdach (Figure 122), succeed by the neurologist Jules B. Luys (1828-1897), who identified in 1865 four centers which he called: *centre antérieur, centre postérieur, centre médian* and *centre moyen* (*Luys, 1865*) (Figure 122).

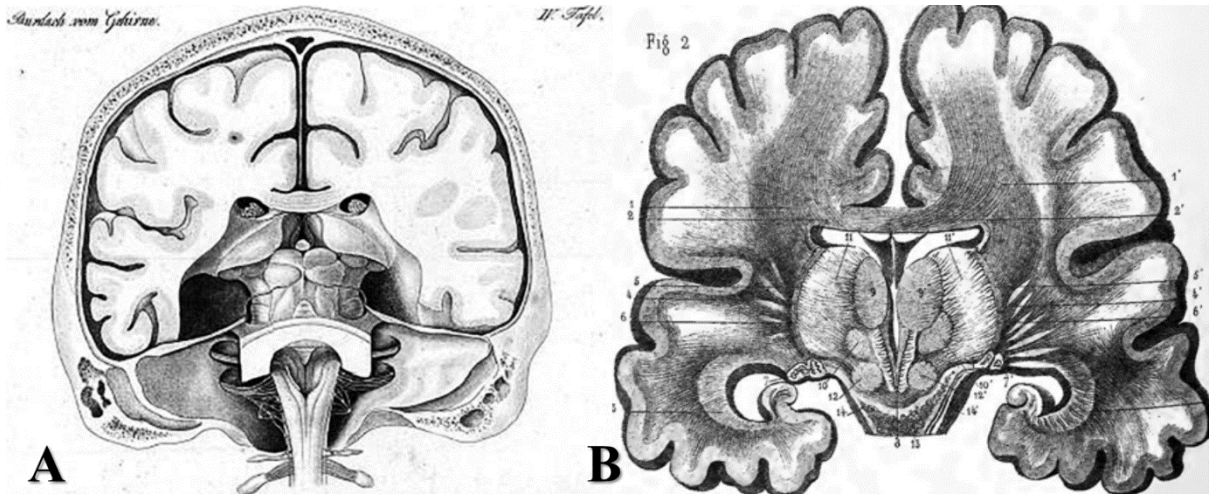


**Figure 122.** Image of thalamus (from *Burdach, 1822*) (A). Coronal section of human brain showing nuclear subdivisions of the thalamus (from *Luys, 1865*) (B). (public domain)

***Claustrum***

The term *claustrum* refers to a barricade and comes from the term *claudere* which means to close (*Turliuc et al. 2017a*). In ancient Rome, the *Claustra Alpium Iuliarum* (Figure 123) was a defense barrier between the Roman Empire and Pannonia designed to guard it against Eastern invaders (*Whittaker, 1997*).

In neuroanatomy, *claustrum* (Figure 123) is a thin layer of grey matter substance between the basal ganglia and insula (Island of Reil) (*Kowianski et al, 1999*). It was later discovered and named *nucleus taeniaeformis* in 1822 by the anatomist Vicq d'Azyr in 1786 (*Déjérine, 1895*) (Figure 123).

We owe the current name of this structure, claustrum, to the German Burdach, who coined the term in 1822 (*Burdach, 1819, Burdach, 1822, Burdach, 1826, Rae, 1954*).

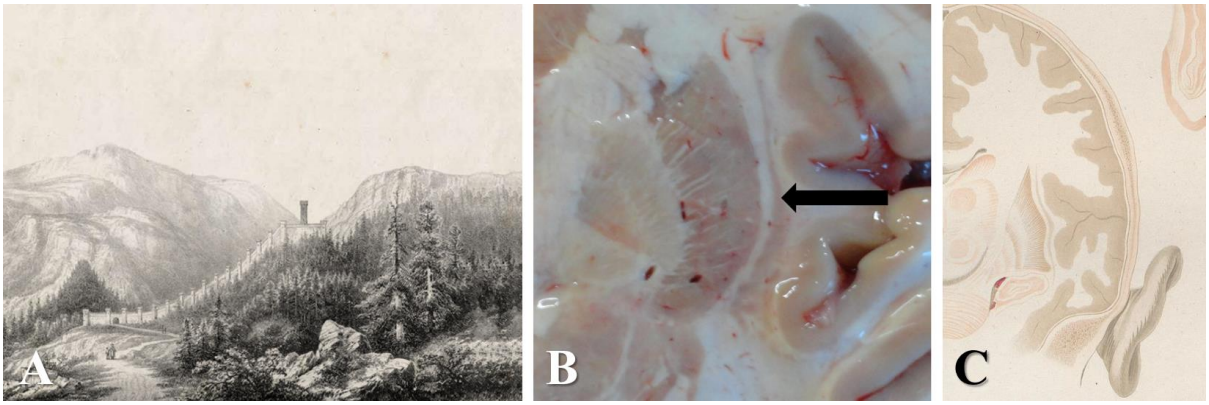


**Figure 123**. Claustra Alpium Iuliarum (public domain) (A). Claustrum (black arrow), *courtesy of Dr. G. F. Dumitrescu* (B). Claustrum drawn in *Traité d'Anatomie et de Physiologie (Vicq D'Azyr F, 1786)* (C). (public domain)

***Fastigium***

In Ancient Rome, *fastigium* represented a triangle-shaped construction element, located on the facades of Roman temples (*Smith and Anthon 1846/2005*) (Figure 124). Due to the similarity with this structure, in 1822, Burdach called the roof of the fourth ventricle *fastigium* (*Arslan, 2014, Swanson, 2014*) (Figure 124).

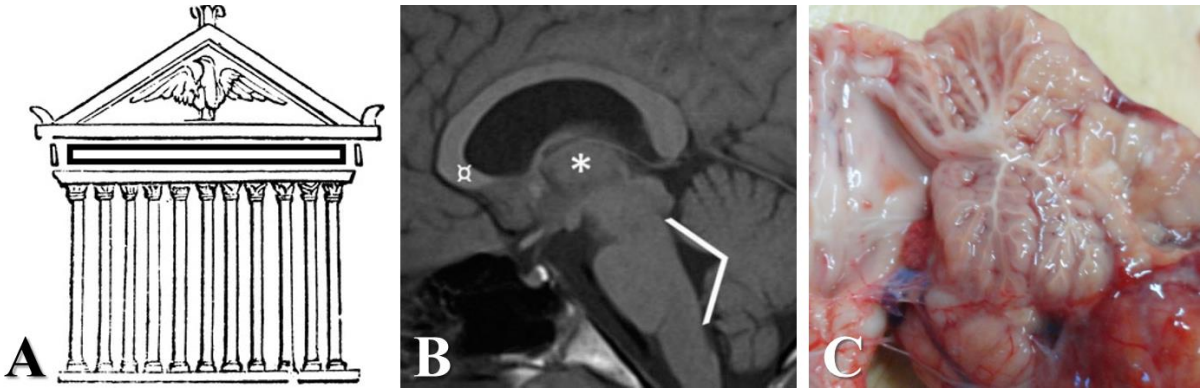


**Figure 124**. Fastigium of the Roman temple (public domain) (A). Sagittal brain section MRI: * thalamus, ¤ rostrum, > fastigium (from *Turliuc et al., 2017a*) (B). Macroscopic anatomical image showing the fastigium (C) (*Courtesy of Dr. G. F. Dumitrescu)*

***Cuneiform lobe***

In Ancient theaters, *cuneus* was the division between two stairway (*Fagan, 2011*) (Figure 125) and inspired anatomists when coining the term *cuneate lobe* (Figure 125). Being located on the medial surface of the occipital lobes, the cuneate lobe was first described in 1543 by the famous anatomist Andreas Vesalius, followed by Samuel Soemmerring (*Turliuc et al., 2017a*). Its current name, *cuneate lobe*, was suggested later, in 1822, by Burdach who also made a detailed description of this lobe (*Meyer, 1970*).

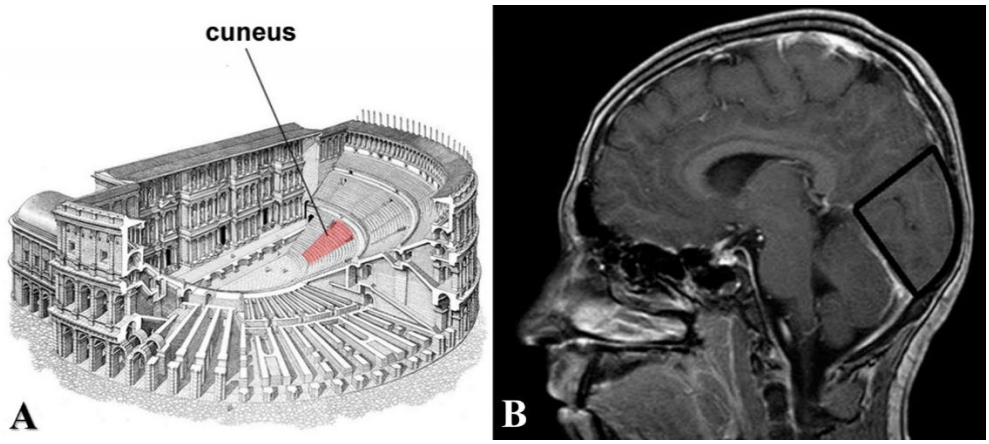


**Figure 125**. One of a set of wedge-shaped divisions separated by stairs in the Ancient theatre, called cuneus (A). Sagittal MRI image showing the cuneiform lobe (black frame) (*Assoc. Prof. Dr. M. D. Turliuc's personal collection*) (from *Turliuc et al., 2017a*) (B).

***Tentorium cerebelli***

Another Roman architectural structure that inspired anatomists was the *tentorium* (*Turliuc et al., 2017a*), which was actually a tent-hut made of high-quality material, which sheltered superiors of the Roman army (*Evans et al., 1873*). This inspired Jacob Winslow (1669-1760) in 1732 to assign the name *tentorium cerebelli* to a dura mater extension covering the hindbrain (*Winslow, 1732*) (Figure 126).

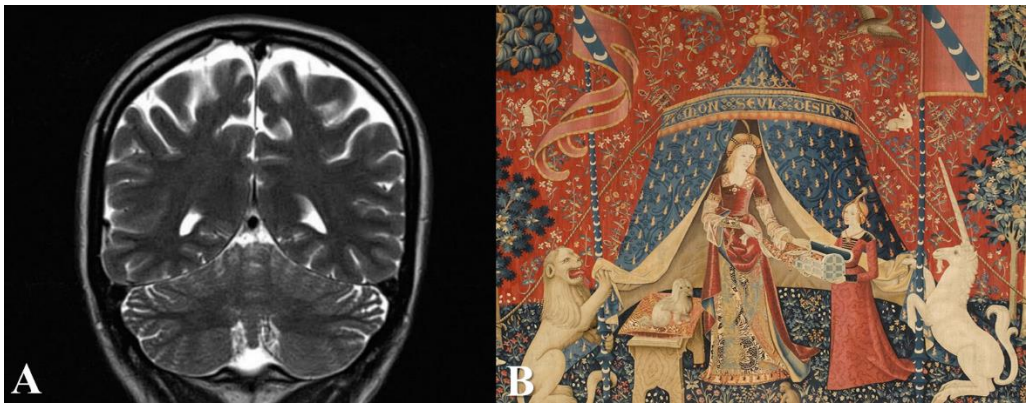


**Figure 126**. Coronal MRI image showing the tentorium cerebelli (from *Turliuc et al., 2017a*) (A). The Lady and the Unicorn, *Tapestry Cycle, late 15th century, National Museum of the Middle Ages, Paris* (public domain) (B).

In conclusion, ancient Romans were not only the founders of well-defined urban living standards, the fathers of rigor, discipline and hygiene, but also the promoters of a superior way of life that also inspired anatomists, which is nowadays reflected in the anatomical terminology.

### I.4.4.3. Clinical neuroanatomy and its importance for neurosurgery

***Background***

Trigeminal neuralgia (TN) was defined as *"a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve"* (*Merskey and Bogduk, 1994*).

The most common cause of TN is the compression of the nerve V, which occurs where the root enters the pons and which may be caused by an artery or a vein (*Love and Coakham, 2001*). The concept of neurovascular compression was first suggested by Walter Dandy in 1934 (*Dandy, 1934*) and several years later, Peter J. Jannetta suggested in 1967 the microvascular decompression of the trigeminal nerve as treatment method (*Love et al., 1998*).

As the importance of clinical neuroanatomy for neurosurgery is one of my research goals, I published two papers on neurovascular compression syndrome in trigeminal neuralgia.

Cucu AI, Costea CF, Sava A, Dumitrescu GF, Turliuc S, Costachescu B, Poeata I, Trandafir V, **Turliuc MD**. *Neurovascular compression syndrome in trigeminal neuralgia*. Revista Română de Anatomie Funcțională și Clinică Macro-și Microscopică și de Antropologie 2018, 17(3):199-203.

**Turliuc D**, Dobrovat B, Cucu A, Turliuc S, Trandafir D, Costea CF. *To be or not to be a neurovascular conflict: importance of the preoperative identification of the neurovascular conflict in the trigeminal neuralgia*. Romanian Neurosurgery 2016, 30(3):334-341.

In the case of neurovascular compression syndrome in the trigeminal nerve, there is an aberrant or redundant looping of intracranial vessels (*Peschillo and Delfini, 2013*), and most commonly, at its exit from the brainstem, the nerve is compressed by the superior and the anterior inferior cerebellar artery (*Adamczyk et al., 2007, Love and Coakham, 2001, Sindou et al., 2002a, Sindou et al., 2002b*) (Figure 127). The compression most frequently occurs in the transition zone of the V nerve (*Love and Coakham, 2001, Love et al., 1998*).

As far as medical imaging methods are concerned, MRI is the most commonly employed (*Lutz et al., 2011*), as, first of all, it identifies the presence or the absence of a neurovascular contact (Figure 127) and, second of all, it rules out other TN causes. The most important MRI sections are: MR angiography 3D TOF and 3D FIESTA (*Docampo et al., 2015, Linn et al., 2009, Yousry et al., 2000*).

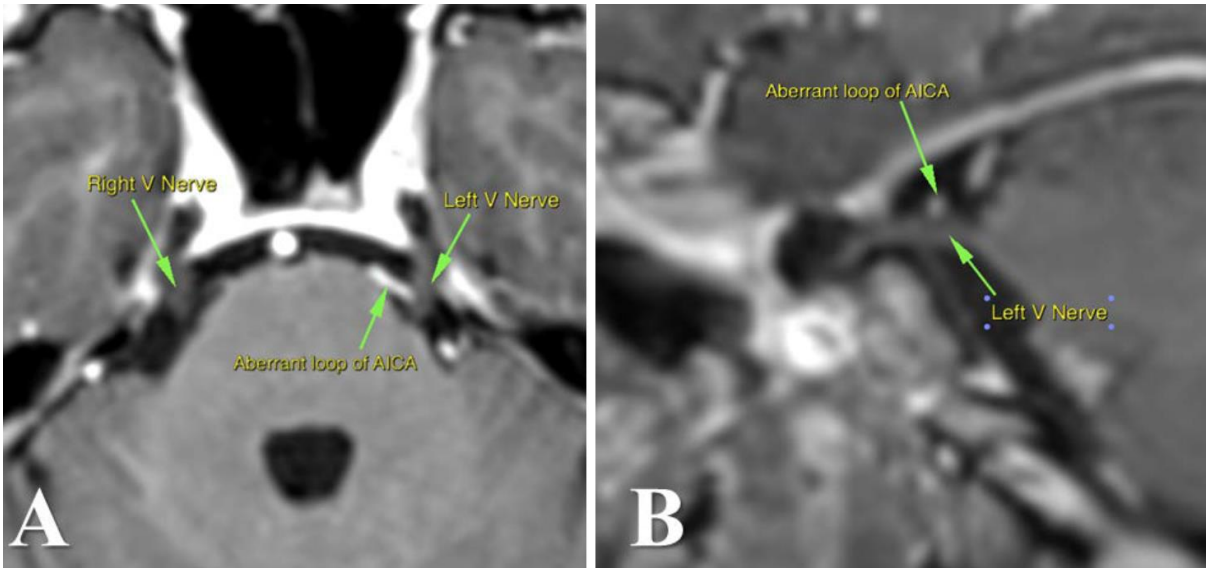


**Figure 127**. "MRI 3DT1 axial (A) and sagittal (B) sections showing the left trigeminal nerve compressed by an aberrant loop of the anterior inferior cerebellar artery; the right trigeminal nerve is normal," *Courtesy of Dr. B. Dobrovat* (from *Turliuc et al., 2016g*)

The neurovascular conflict may be classified in three degrees: (1) contact between the trigeminal nerve and a vessel, (2) artery displacing the trigeminal nerve and (3) artery indents the trigeminal nerve with its thinning (*Harsha er al., 2012, Turliuc et al., 2016g*).

Among MRI, the diffusion-tensor imaging with tractography has recently come to assess white substance integrity of the trigeminal root by *in vivo* measurement of diffusivity (*Becker et al., 2008, Herweh et al., 2007, Le Bihan, 1995, Lutz et al., 2011*), and this sequence practice determines the degeneration and damage of the V nerve (*Basser and Pierpaoli, 1996, Moseley et al., 1990)*.

The indication for surgery should be set correctly and properly, as studies report the absence of intraoperative neuro-vascular compression in 4 - 89% of cases, with a mean percentage of 7.5% (*Kuncz et al., 2006*). Moreover, some authors argue that even in cases where no neurovascular conflict was detected during surgery manipulation of nerve root with minimum trauma had a positive consequence on patients with trigeminal neuralgia (*Baechli and Gratzl, 2007, Ma, 2009, Zakrewska et al., 2005*).

In conclusion, in the case of TN caused by neurovascular conflict, it is extremely important to be capable to identify the compression syndrome on the imaging findings, in order to give a correct surgical indication. Preoperative imaging studies are also needed not only to accurately identify neurovascular compression, but also to exclude other causes of TN (*Cucu et al., 2018e, Turliuc et al., 2016g*).

# I.5. Interference of neurosurgery with neurosciences

## I.5.1. Psychological implications and ethical aspects of neurosurgery

***Background***

The vast majority of people, following exposure to traumatic events throughout their lives, may develop one of the symptoms of posttraumatic stress disorder (PTSD) such as avoidance, hyperarousal, intrusion or negative cognitions (**American Psychiatric Association 2013*). Moreover, over the past 20 years, various authors have reported that exposure to traumatic events or to their victims has led to PTSD (*Caine and Ter-Bagdasarian, 2003, Figley, 1995, McCan and Pearlman, 1990*). Work in relation to traumatic stress may be affected in the sense that the quality of work-related activities may be negatively influenced by them.

*In the field of psychological implications in neurosurgery and stress factors influencing neurosurgeons, I have published 1 original paper in a journal indexed in ISI Web of Science and 4 papers in journals indexed in other international databases and the summary of the most important data are presented here, in the followings:*

Turliuc MN, Mairean C, **Turliuc MD**. *Rumination and suppression as mediators of the relationship between dysfunctional beliefs and traumatic stress.* International Journal of Stress Management 2015, 22(3):306-322. (Impact Factor in 2015 = 1.389)

*This paper has 4 ISI citations.*

**Turliuc DM**, Costea CF, Turliuc S, Sascau RA, Patrascanu E, Poeata I, Cucu AI. *The lion heart of a neurosurgeon: the stress during a life of neurosurgery*. Romanian Neurosurgery 2018, 32(2): 211-216.

**Turliuc DM**, Turliuc S, Cucu AI, Costea CF. *Professional envy among doctors.* Romanian Journal of Oral Rehabilitation 2016, 8(3):80-85.

*This paper has 1 citation.*

Tamas I, Tamas C, Enasoae I, **Turliuc D**. *Illness and healing in the Holy Scripture. Church serving the elderly and sick: bioethics for care people suffering from neuro-degenerative diseases, primary and metastatic brain tumors*. Romanian Journal of Bioethics 2015, 13(3):1-11.

**Turliuc D**, Turliuc S, Cucu A, Buraga V, Costea CF. *Claiming dignity while dangling between life and death*. Romanian Journal of Artistic Creativity 2015, 3(1):34-38.

### I.5.1.1. Rumination and suppression and the relation between dysfunctional beliefs and posttraumatic stress

***Background***

Being interested in the effects of stress on neurosurgery staff, we conducted a study on 138 doctors and nurses, including on neurosurgery staff, in which we investigated traumatic stress, more precisely weather dysfunctional beliefs about the self and the surroundings, rumination and suppression contributes to PTSD occurrence in Romanian healthcare staff (*Turliuc et al., 2015c*).

***Material and Methods***

The research was conducted in 3 hospitals in the city of Iasi (Romania), and included 138 medical workers from several fields of medicine: neurosurgery, emergency, intensive care, oncology and ambulance. Of these, the highest proportion, 26.08%, was represented by doctors and nurses in the neurosurgical field (n = 36). Most of the participants were women (79%). Also, their ages ranged from 25 to 66 years, with a mean age of 39.11 years (SD = 9.48). All participants answered a set of questionnaires after signing the confidentiality consent (Table 32).

The following scales were used as measures: Traumatic Stress Institute Belief Scale (TSI-BLS) (*Pearlman, 1996*), Secondary Traumatic Stress Scale (STSS) (*Bride et al., 2004*) and Response to Intrusion Questionnaire (RIQ) (*Clohessy and Ehlers, 1999, Murray et al., 2002*).

**Table 32**. Demographic and professional characteristics of participants (from *Turliuc et al., 2015c*)

| | *n* | % | *M* | *SD* |
|---|---|---|---|---|
| Age | | | 39.11 | 9.48 |
| Experience (years) | | | 10.50 | 9.68 |
| Gender | | | | |
| Female | 109 | 79 | | |
| Male | 29 | 21 | | |
| Profession | | | | |
| Physicians | 49 | 35.5 | | |
| Nurses | 89 | 64.5 | | |
| Field of practice | | | | |
| Intensive care | 31 | 22.46 | | |
| Emergency | 29 | 21.01 | | |
| Ambulance | 19 | 13.76 | | |
| Neurosurgery | 36 | 26.08 | | |
| Oncology | 23 | 16.66 | | |

*Note*. $N = 138$.

***Results***

As a preliminary analysis, to test for a possible bias, we conducted an independent samples t-test comparing the professional approach to intrusions, suppression, dysfunctional beliefs and rumination (nurses vs. doctors), with no significant differences on any study variables (Table 33).

Pearson's correlation also proved that dysfunctional beliefs and intrusions are positively

correlated (r=.44, p<.001), just as dysfunctional beliefs and each rumination and suppression (rs=.33 and .40, p<.001). Moreover, our research proved that intrusions are significantly correlated with rumination and suppression (rs=.42 and .41, p<.001) (*Turliuc et al., 2015c*) (Table 33).

**Table 33**. Pearson's correlations, means, standard deviations (SDs) and Cronbach's Alphas (in bold on the diagonals) of study variables (from *Turliuc et al., 2015c*)

| | *M* | *SD* | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| 1. Dysfunctional beliefs | 110.58 | 16.44 | **.92** | | | |
| 2. Rumination | 7.54 | 3.03 | .33** | **.82** | | |
| 3. Suppression | 5.51 | 2.81 | .40** | .51** | **.74** | |
| 4. Intrusions | 11.96 | 3.27 | .44** | .42** | .41** | **.77** |

*Note.* $N = 138$.
** $p < .001$.

***Discussions***

In the last two decades, the Romanian healthcare system has been the victim of poor management, a shortage of medical staff and recently a massive migration of doctors and nurses. This research has provided evidence of the relationship between dysfunctional cognitive assumption and work-related PTDS.

Suppression of unwanted thoughts and rumination provides a good explanation of this relationship, all the more so as the results are not surprising, since the participants to this study work under extreme stress, and have witnessed distressing scenes, which made them sad and caused emotional damage.

Romanian healthcare staff in general is subject to a large workload that requires a lot of energy and may lead to burnout syndrome. As a result, in order to achieve their professional goals, doctors and nurses may need to suppress their own emotions (*van Gelderen et al., 2011*). However, workers who find it difficult to cope with traumatic memories should know that suppression of emotions, i.e. avoidance of unwanted thoughts, is counterproductive, especially since it increases sympathetic activity (*Gros and Levenson, 1997*) and reduces cardiac sympathetic activity control (*Demaree et al., 2006*).

As a conclusion, we believe that medical workers need support to cope with the traumatic events that witnessed during service, all the more so as there is a fine line between the professional distance necessary to prevent overwhelming work emotions and emotional detachment and suppression related to PTSD (*Turliuc et al., 2015c*).

Identifying individuals at particularly high risk of PTSD would be the first step in the implementation of stress management services. Our study sheds some light on the mechanisms by which dysfunctional beliefs may influence traumatic stress and underlines the importance of the analysis of several vulnerability factors in an attempt to understand PTSD etiology (*Turliuc et al., 2015c*).

### I.5.1.2. Stress and professional envy among neurosurgeons and their consequences on their work

In neurosurgery there are many challenges and factors that can disrupt doctors' work, the most common of which are stress and professional envy among colleagues (*Turliuc et al., 2018b, Turliuc et al., 2016h*).

Due to the many technical requirements, surgical challenges and time pressure, surgeons work in a stressful environment (*Georgiou et al., 2017*) which affects them and also has direct effects on patient outcomes (*Gurman et al. 2012, Wong et al., 2010*). Thus, McAbee *et al.*, in a nationwide study from America, reported that 57% of USA brain surgeons suffered from burnout syndrome (*McAbee et al., 2015*). Also, residents in neurosurgery work harder than other residents, more precisely about 10% more than the 80-hour weekly limit for the other specialties (*Muscatello et al., 2006*).

As for their degree of satisfaction, the most unsatisfied surgeons are those who have no time for personal life and family (*Balch, 2011a, Balch, 2011b, Balch, 2011c, Shanafelt and Dyrbe, 2012*), at the opposite pole being those who have time for their personal activities, (*Balch, 2011a, Balch, 2011b, Balch, 2011c, Kuerer et al., 2007*), those who teach in the higher education system (*Balch, 2011b, Balch 2011c*) or those who operate a lot (*Shanafelt et al., 2009*). In the same study, McBee proved that intellectual stimulation, having the right balance between carrier and personal life, being surgically productive and having children are factors which increase a neurosurgeon's satisfaction (*McAbee et al., 2015*).

In conclusion, finding factors that increase the neurosurgeon's personal satisfaction and reduce mental stress will improve performance and also increase patient safety.

Another disruptive factor in the work of neurosurgeons and doctors in general is professional envy, which is based on the feeling of pride. This represents the desire for self-centered affirmation that leads to belittling of the qualities of others and which is based on the exacerbation of the desire for personal affirmation without discerning one's own value (*Turliuc et al., 2016h*).

Ferriani Signor published a study on professional envy in 2004, in which he made a ranking of the professions the most exposed to professional envy and jealousy. Architects were at the bottom, followed by lawyers and military officers, university professors of science and literature, journalists, authors of books, doctors and actors at the top of the pyramid (Figure 128).

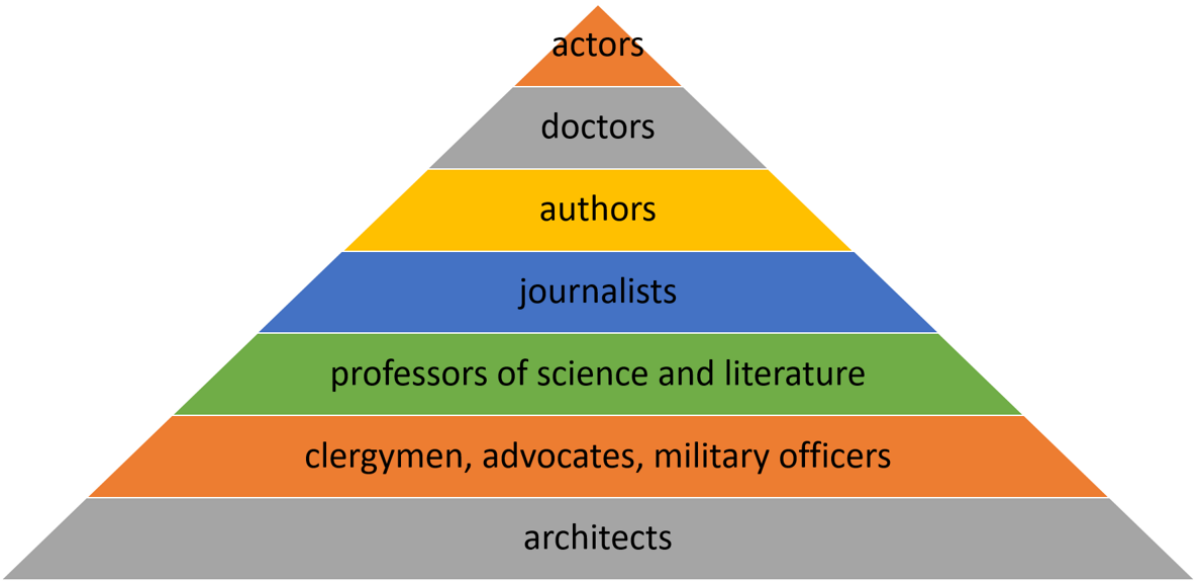


**Figure 128**. Pyramid of professional envy (after *Ferriani, 2004*)

As concerns professional envy, the author of the study has shown that doctors have a bad reputation in this regard. The reason for which doctors rank almost highest in the pyramid is explained by their personal feelings that are intensely involved in the confrontational environment in which they work. The author also points out that doctors suffer from close personal rivalry, with degrading consequences (*Ferriani, 2004*).

Envy (Figure 129) emerges when 3 conditions are met: negative perception of self and feeling of frustration, existence of the relevance of this perception for self-definition and similarity with another person (*Salovey and Rodin, 1984*). As far as professional envy among surgeons is concerned, we have distinguished between surgical envy itself, hierarchical envy and patient-related envy (*Turliuc et al., 2016h*).


**Figure 129**. Mad woman with a mania of envy (c.1819/1822), *Théodore Géricault (1791-1824), Museum of Fine Arts of Lyon* (A). Minerva and Saturn protect Art and Science of envy and falsehood (1644), *Joachim von Sandrart (1606-1688), Museum of Fine Arts, Vienna* (B). (public domain)

The best predictor of envy is the importance of the field for the individual's ego. If a subject has a big discrepancy in terms of his real and ideal professional fulfillment, the doctor will be more likely to envy one of his colleagues. Also, the phenomenon of comparison and similarity occurs in envy especially with others whose similar characteristics are relevant for their fields of definition (*Festinger, 1954*).

Ferriani suggests self-discipline, cultivation and practice of a noble profession and the pursuing a high ideal in life as remedy to professional envy among doctors.

Another problem encountered in neurosurgical ethics and in current practice is the neurosurgeon's decision to operate on patients with severe head injuries (*Turliuc et al., 2015d*). In this respect, statistical studies have reported that the most important factors that influence the doctor's decision to operate or not on a patient outside the surgical resources are the doctor's prejudices, the family preferences, the emotional burden of the family and the doctor, and also the medical protocols (*Tversky and Kahneman, 1974*).

Although various studies have tried to find predictive factors in patients with severe head injuries, taking into account the trauma mechanism, GCS, patient's clinical data, age, neuroimaging findings, time to surgery (*Hemphill et al., 2001*), it seems that among these the patient's age is the most important prognostic factor (*Lingsma et al., 2010*). However, the doctor's decision to operate on a patient with severe head injury is extremely difficult to make, the doctor being forced to choose between doing nothing and the risk of doing too much, by taking additional and unnecessary actions (*Honeybul et al., 2011, Turliuc et al., 2015d*). Despite all these aspects, however, the quality of life is a major issue that outshines the doctor's decision-making factors (*Ubel et al., 2005*).

As regards the decision to operate on patients with brain tumors, the therapeutic approach is based on brain tumor histology and illness prognosis, and it should also focus on the patient's postoperative life quality, not only on his survival (*Tamas et al., 2015*).

In the last period, there has been an increasing recognition of palliative care offered to patients, precisely for improve the quality of life. The World Health Organization defines palliative care as *"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening disease patients through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, both physically, psychologically and spiritually"* (*Wellisch et al., 2002*). Thus, the treatment of patients with cerebral tumors includes not only good relationship, but also psychological counseling and rehabilitation services. These patients have a particular demand for communication and involvement skills in assisting them and other family members (*Tamas et al., 2015*).

### I.5.2. Forensic and psychological aspects in neuro-ophthalmology

***Background***

Estimated 1.6 million people are losing their visual acuity each year, with a frequency peak among young adults and aged individuals (*Glynn et al., 1988, Desai et al., 1996, MacEwen, 1999, Nadeem et al., 2013*). Among the many causes, eye injury represents a critical cause of morbidity

worldwide. Also, one in twenty patients goes to the ophthalmologist due to an eye injury, these situations having social, economic but also forensic impact (*MacEwen, 1999*).

*In the field of forensic and psychological implications in neuro-ophthalmology, I have published 3 papers in journals indexed in international databases and the summary of the most important data are presented here, in the followings:*

Costea CF, Sava A, Dumitrescu GF, Mircea A, Cucu A, Turliuc S, **Turliuc D**. *Forensic aspects of ocular trauma*. Aperito Journal of Ophthalmology 2015, 1 (2):1-5.

Costea CF, **Turliuc D**, Sava A, Dumitrescu GF, Cucu A, Turliuc S. *Principles and guidelines involved in the management of surgical acquired anophthalmia patients*. Romanian Journal of Oral Rehabilitation 2016, 8(1):59-64.

Costea CF, Cucu AI, Dimitriu G, Brosteanu M, Turliuc S, Dumitrescu GF, Sava A, **Turliuc MD**. *Understanding the psychological impact in a clinical case of eye globe rupture with forensic implications.* Romanian Journal of Oral Rehabilitation 2016, 8(2):61-67.

***Materials and methods***

We performed a retrospective study on a number of 109 patients with eye injury hospitalized between 2010 and 2012 in the Department of Ophthalmology at Prof. *Dr. Nicolae Oblu* Emergency Clinical Hospital in Iași, Romania. We considered the demographic and anamnestic data of these patients, and analyzed their age, gender, type of injury and eye structures involved (*Costea et al., 2015a*).

***Results and discussions***

1.59% of the 6839 patients hospitalized in the Department of Ophthalmology between 2010 and 2012 had suffered eye injuries (Figure 130). Men accounted for more than half of these, with a percentage of 76.14% (*n = 83*), the male/female ratio being 3.1.

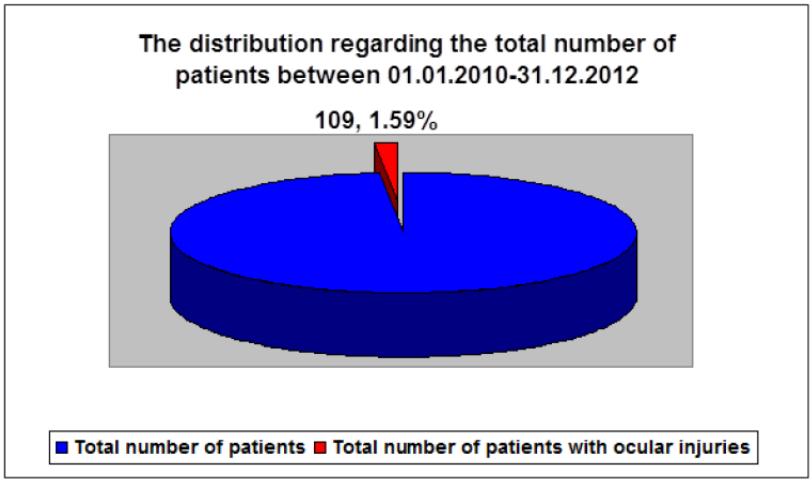


**Figure 130.** Percentage of patients with eye injuries over a period of 3 years (from *Costea et al., 2015a*)

Both eyeballs were impaired almost to the same extent, with 53.22% of injuries occurring in the right eyeball and 46.78% in the left eyeball, and with a slight predominance of the right eyeball. As far as eye injury according to the etiological mechanism is concerned, penetrating or perforating eye injuries that required eyeball reconstruction were the most common (88.07%) (*Costea et al., 2015a*) (Table 34).

**Table 34**. Types of eye injury according to the etiological mechanism (from *Costea et al., 2015a*)

| Type of ocular trauma | Number of cases (%) |
|---|---|
| Penetrating/perforating trauma | 96 (88.07) |
| Non-penetrating trauma | 6 (5.50) |
| Penetrating/perforating trauma with intraocular foreign body | 7 (6.43) |

Concerning ocular structure impairment, the most frequent occurrences in our clinic were corneal wound and traumatic cataract, associated to lesions of the sclera and iris (Table 35). In a similar study, Parmar *et al*. reported the cornea (47.60%), iris (32.64%) and eyelids (25%) to be the most frequently impaired eye structures in case of eye injury (*Parmar et al., 1985*). The cornea was also the most frequently impaired in our study (*Costea et al., 2015a*).

**Table 35**. Patterns of eye injury according to the impaired eye structures (from *Costea et al., 2015a*)

| Structural damage to the eyeball | Number of cases |
|---|---|
| Eyelid wound | 2 |
| Conjunctival wound | 11 |
| Corneal abrasion /corneal ulcer | 3 |
| Corneal leucoma | 13 |
| Corneal siderosis | 1 |
| Corneal wound | 39 |
| Corneo-scleral wound with iris hernia | 11 |
| Corneal wound with iris hernia | 12 |
| Scleral wound | 28 |
| Traumatic cataract | 48 |
| Dislocation / subluxation of the lens | 5 |
| Irido-dialysis / iris coloboma | 3 |
| Traumatic exogenous uveitis | 20 |
| Hyphaema | 3 |
| Secondary Glaucoma | 10 |
| Vitreous bleeding | 5 |
| Retinal detachment | 9 |
| Macular edema | 1 |
| Hemophtalmus | 14 |
| Endophtalmitis | 5 |
| Traumatic optic neuropathy | 1 |
| Eyeball atrophy | 3 |
| Orbital cellulitis | 2 |

All penetrating or non-penetrating eye injuries that results in loss of an organ have as an effect facial disfigurement or post-traumatic consequences, such as entropion, ptosis, and strabismus and has legal implications, the author being convicted based on the severity of these injuries (*Sharma et al., 2008*).

In forensic cases of eye injury, the patient's assessment needs to be accurate and right documented in order to examine visual acuity, pupillary reflexes and oculomotility. Among paraclinical methods, direct ophthalmoscopy, fluorescein test, ocular ultrasound, CT and MRI scan should be taken into account (*Pokhrel and Loftus, 2007*).

In Romania, the loss of the eyeball or of the visual acuity is a serious injury, and the Romanian Penal Code provides 2 to 10 years of imprisonment as punishment, because the assault resulted in the loss of a sense organ and a permanent physical defect (*Antoniu et al., 2011*).

The loss of an eye, beyond its forensic implications, has first and foremost strong psycho-emotional implications, often apocalyptic for patients, regardless of gender, age, social status, intellect or age. In these cases, the ophthalmologist, neurosurgeon and plastic surgeon must be aware of Beauchamp and Childress' four bioethical principles (the patient's autonomy, non-maleficence, principle of justice and beneficence) and apply them to patients with surgically acquired anophthalmia (*Costea et al., 2016*).

Eye injury cases are emergencies and require immediate treatment (Figure 131). In forensic cases, we recommend the detailed documentation and examination, so that the forensic evidence is sufficient, careful, correct and meticulous to correctly classify the crime according to the Penal Code (*Costea et al., 2015a*).

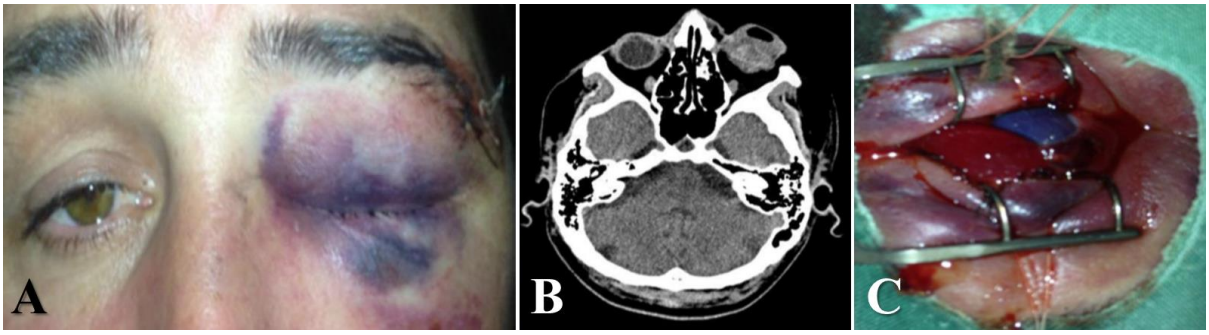


**Figure 131**. Preoperative appearance: eyelid hematoma, traumatic ptosis and left eyebrow wound (A). Axial CT scan showing complete destruction of the left eyeball (B). Operating microscope view of an eyeball rupture secondary to blunt trauma with a metallic blunt object. Subconjunctival hemorrhage of this severity raised suspicion of eyeball rupture (C) (from *Costea et al., 2016a*)

Mental infirmity is one of the consequences of eye injury, all the more prevalent in the case of surgically acquired anophthalmia. This may range from anxiety and acute post-traumatic stress to depressive episodes and suicidal ideation (*Costea et al., 2016a*).

### I.5.3. Research on cerebrovascular diseases

#### I.5.3.1. Morphopathological particularities of cerebrovascular diseases for patients in the northeastern area of Romania

***Background***

In industrialized countries, cerebrovascular disease is the first cause of acquired disability, the second cause of dementia and the third cause of mortality, and in our country, according to Cinteza *et al.*, cerebrovascular disease has a prevalence of 13.9% in people over 70 years of age (*Cinteza et al., 2007*).

*We have conducted two retrospective studies of the morphopathological specificity of patients with cerebrovascular diseases in North-eastern Romania and of the particularities of using contrast agents in stroke, and the findings were published in 2 journals indexed in ISI Web of Science and the summary of the most important data are presented here, in the followings:*

Cuciureanu ID, Hînganu MV, Stătescu C, Sava A, Hînganu D, **Turliuc MD**, Cuciureanu T, Sascău RA. *Morphopathological particularities of cerebrovascular diseases for patients in the northeastern area of Romania*. Romanian Journal of Morphology and Embryology 2019, 60(1):227-232. (Impact Factor in 2018 = 1.5)

*This paper has 1 citation.*

Cuciureanu DI, Statescu C, Sascau RA, Cuciureanu T, Constantinescu VA, Hinganu D, Preda C, Hinganu MV, **Turliuc MD**. *Particularities of using contrast agents in diagnosis of stroke*. Rev Chim (Bucharest) 2019, 70(2):685-688. (Impact Factor in 2018 = 1.605)

*This paper has 10 ISI citations.*

***Material and Method***

Our study was conducted on a number of 70 patients hospitalized at *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital of Iași and diagnosed with ischemic stroke with spontaneous hemorrhagic transformation and monitored between 2015 and 2018.

Demographic data, medical history, comorbidities, as well as risk factors (atrial fibrillation, neoplasms, arterial hypertension, diabetes, dyslipidemia, renal pathology, venous disease and mutations of Factor V Leiden) were collected. We have also recorded data on alcohol consumption, smoking and also systolic and diastolic blood pressure. All patients were evaluated by computed tomography scanning, which revealed the size and localization of the infarcted region, the mass effect, signs of hemorrhagic transformation and the existence of sequellary infarction. In the patients who died, the anatomopathological examination from brain lesions was performed (*Cuciureanu et al., 2019*).

***Results***

Most patients included in our study had associated cardiovascular risk factors like: 72.85% - arterial hypertension, 68.57% - dyslipidemia, 57.14% - atrial fibrillation, 28.57% - history of stroke

and 21.42% - diabetes mellitus (Figure 132). Also, 48.57% of the patients had 3 or 4 associated risk factors (*Cuciureanu et al., 2019*).

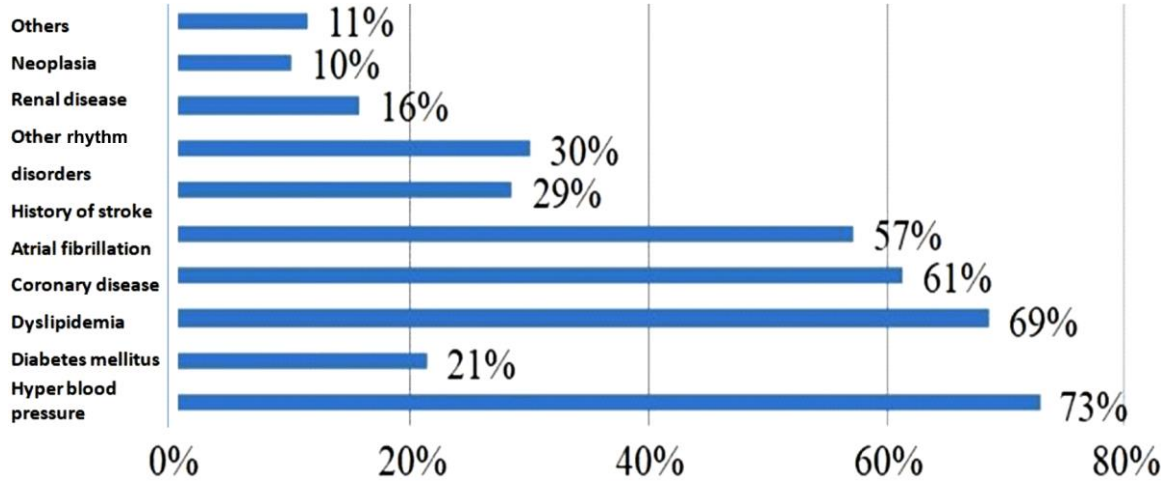


**Figure 132**. Risk factor distribution in sample group (from *Cuciureanu et al., 2019*)

Of all 70 patients, 51 suffered an ischemic stroke and 19 a hemorrhagic stroke, and hemorrhagic transformation occurred in 10 patients. Motor deficit occurred in 94.28% of the cases (Table 36).

**Table 36**. Main and associated neurological signs at admission (from *Cuciureanu et al., 2019*)

| Clinical neurological picture at admission | | | Associated neurological signs | | |
|---|---|---|---|---|---|
| ***Variable*** | ***No. of patients*** | ***Percent*** | ***Variable*** | ***No. of patients*** | ***Percent*** |
| *Glasgow Coma Scale (GCS)* | 14–52 | 74.28% | *Dysarthria* | 6 | 8.57% |
| | 15 | 21.42% | *Hemianopsia* | 24 | 34.28% |
| | 8–13 | 4.28% | *Hemihypoesthesia* | 15 | 21.42% |
| | 0–7 | 3% | *Vertigo* | 7 | 10% |
| *Aphasia* | 35 | 50% | *Cephalia* | 16 | 22.85% |
| *Motor deficiency* | 66 | 94.28% | *VI$^{th}$ nerve paresis* | 51 | 72.85% |
| *Visual field disorders* | 2 | 2.85% | *Conjugate deflection of the eyeball* | 3 | 4.28% |
| | | | *Signs of atherosclerosis* | 36 | 51.42% |
| | | | *Others* | 20 | 28.57% |

In our study we found that early identification of complications positively influences mortality (Table 37).

**Table 37**. Frequency of complications (from *Cuciureanu et al., 2019*)

| Stroke complications | | | Simultaneous complications | No. of patients |
|---|---|---|---|---|
| ***Variable*** | ***No. of patients*** | ***Percent*** | | |
| *Respiratory tract infection* | 17 | 24.28% | *0* | 21 |
| *Urinary infection* | 12 | 17.14% | *1–2* | 39 |
| *Swallowing disorders* | 13 | 18.57% | *3–4* | 10 |
| *Electrolyte disturbance* | 22 | 31.42% | | |
| *Epilepsy* | 2 | 2.85% | | |
| *Urinary incontinence* | 7 | 10% | | |
| *Depression* | 7 | 10% | | |
| *Cerebral edema* | 12 | 17.14% | | |

As concerns the closed arterial branch and area of stroke, the right medial cerebral artery was involved in 45.71% of the patients (*n=32*), the left medial cerebral artery in 34.28% of the patients (*n=24*), followed by posterior cerebral artery with a percentage of 22.85% (*n=16*) (Table 38).

**Table 38**. Distribution of patients by closed arterial branch (from *Cuciureanu et al., 2019*)

| Area of stroke | No. of patients | Percent |
|---|---|---|
| *Carotid territory* | 2 | 2.85% |
| *Anterior cerebral artery* | 2 | 2.85% |
| *Right medial cerebral artery* | 32 | 45.71% |
| *Left medial cerebral artery* | 24 | 34.28% |
| *Posterior cerebral artery* | 16 | 22.85% |
| *Vertebro-basilar system* | 1 | 1.42% |
| *Cerebellar* | 3 | 4.28% |
| *Anterior carotid artery* | 3 | 4.28% |

In the patients who died, all strokes were embolic, and the pathological examination identified the appearance of liquefactive necrosis (Figure 133).

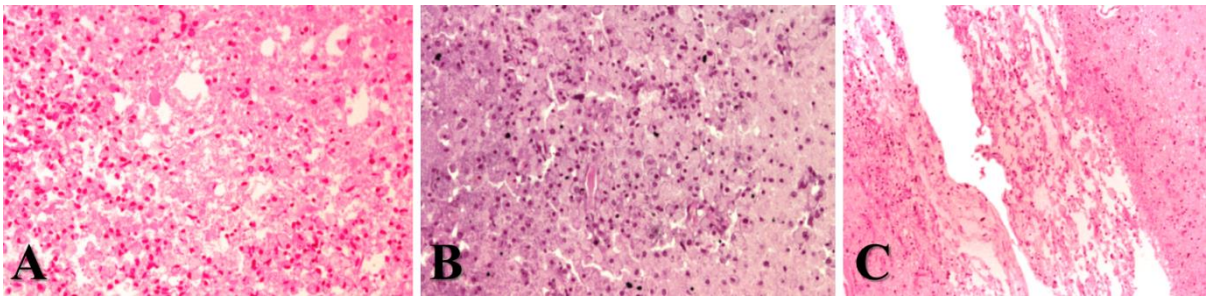


**Figure 133**. Liquefactive necrosis surrounded by lipid-laden macrophages that ingested the products of degradation of dead neurons and myelin (HE staining, ×200) (A). Foamy macrophages that cleaned up the lipid debris from the liquefactive necrosis and newly formed capillary vessels (HE staining, ×200) (B). Resolution of the liquefactive necrosis led to a cystic area surrounded by foamy macrophages, rare fibroblasts, rare lymphocytes, and few new capillary vessels. The nervous tissue around the cavity expressed reactive astrogliosis (HE staining, ×100) (C). *Courtesy of Dr. G. F. Dumitrescu* (from *Cuciureanu et al., 2019*)

***Discussions***

The objective of this research was to identify correlations between risk factors in our population, which would have high stroke potential. In our study we noticed that the predominant localization of stroke was right or left middle cerebral arteries and that there were no bilateral ischemic strokes in the cerebral territory of these arteries. As concerns the associated risk factors, hyperglycemia is considered damaging for cerebral metabolism and may be a predictive factor for hemorrhagic transformation. Also, in our study we found that atherosclerosis and dyslipidemia are the main risk factors in right middle cerebral artery ischemia.

In conclusion, the pathological mechanisms of strokes are determined by risk factors and patient comorbidities, which have a clear demographic pattern. Moreover, the existing correlations between the demographic risk factors of cerebrovascular disease and the symptoms enable specialists to develop a protocol that would lead to a more rapid diagnosis (*Cuciureanu et al., 2019*).

Another study was conducted on a number of 165 patients with different forms of ischemic stroke admitted to *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital between 2014 and 2018. The epidemiological, clinical and etiopathogenetic data, as well as the paraclinical findings were analyzed (*Cuciureanu et al., 2019a*).

49.70% of all cases (*n=82*) were atherosclerotic stroke, 47.27% (*n=78*) embolic stroke and 3.03% (*n=5*) hemorrhagic stroke. The patients were aged 25 to 50 years, and 58% of them were men and 42% women.

As for patients with atherosclerotic disease, in 92.13% of the cases, the strokes occurred in the territory of the internal carotid artery (Figure 134), and most of the hemorrhagic strokes (80%) occurred in the territory of the internal carotid artery (*Cuciureanu et al., 2019a*) (Figure 135).

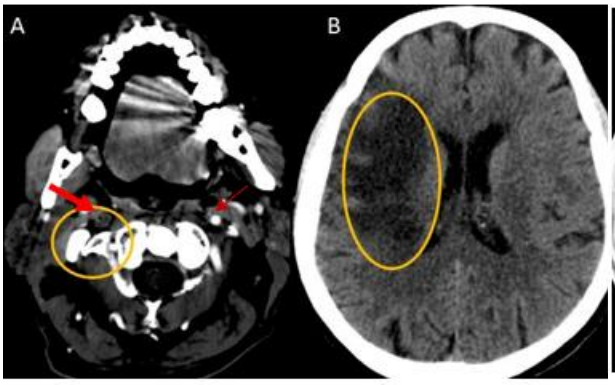


**Figure 134**. Stroke caused by plaque occlusion of the right common carotid artery (A), Native CT scan that highlights the affected brain territory (B) (from *Cuciureanu et al., 2019a*)

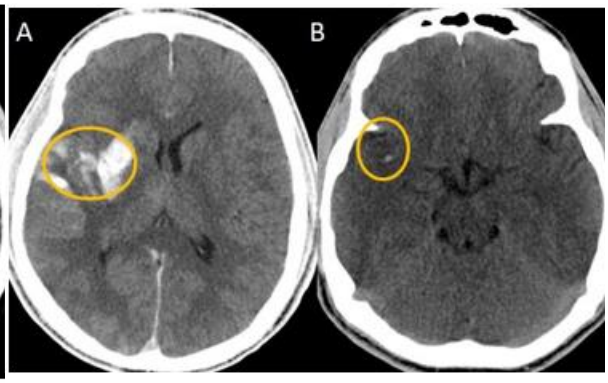


**Figure 135**. Head CT scan in a patient with hemorrhagic vascular accident with contrast substance (A) and native (B) (from *Cuciureanu et al., 2019a*)

As far as the safety of the administration of iodinated contrast agents used in CT scan and MRI is concerned, there are many studies according to which this could disrupt the effect of thrombolytic medication, but this theory has not been proven yet (*Cuciureanu et al., 2019a*).

### I.5.3.2. Particularities of subarachnoid hemorrhage: case studies

**Turliuc DM**, Costachescu B, Poeata I, Dobrin N, Cucu AI, Sava A, Dumitrescu G, Costea CF. *Late diagnosed PHACE syndrome by aneurysmal subarachnoid hemorrhage. Case report.* Revista Medico-chirurgicală a Societății de Medici și Naturaliști din Iași 2017, 121(3):562-567.

**Turliuc D**, Sorete Arbore R, Dobrin N, Chiriac A, Ermalai N. *Subarachnoid hemorrhage in a*

*young patient with a factor V Leiden thrombophilia: case report and literature review.* Romanian Neurosurgery 2013, 20(2):170-179.

### I.5.3.2.1. Late diagnosed PHACE syndrome by aneurysmal subarachnoid hemorrhage

We report here the case of a 58-year-old female patient admitted in Department of Neurosurgery at *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital Iasi for intracranial hypertension syndrome with severe cephalgia. Her clinical examination revealed a facial hemangioma at the level of the left eye, chin and left cheek (Figure 136). Also, on her left cheek we noticed the presence of a heart-shaped scar due to a free skin graft mentioned in the patient's personal medical history (*Turliuc et al., 2017b*).

Computed tomography and computed tomography angiography of the head and 3D reconstructions diagnosed a subarachnoid hemorrhage (Figure 137) with cerebral vascular dysplasia, a ruptured aneurysm of right posterior communicating artery (Figure 138) and an unruptured aneurysm of junction P1-P2 of the left posterior cerebral artery (Figure 139).

**Figure 136**. Facial hemangioma in the distribution of segments 2 and 3 (from *Turliuc et al., 2017b*)

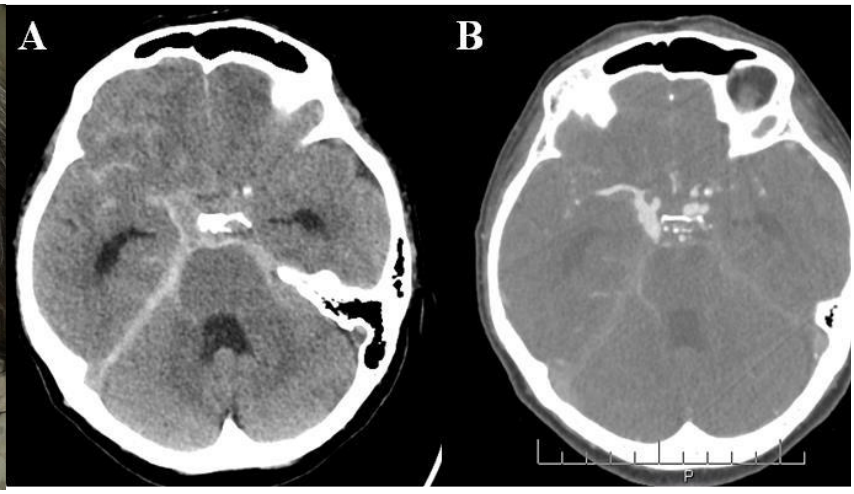


**Figure 137**. Head CT scan with aneurysmal subarachnoid hemorrhage (A). CT angiography showing vascular dysplasia and right posterior communicating artery aneurysm (B) (from *Turliuc et al., 2017b*)

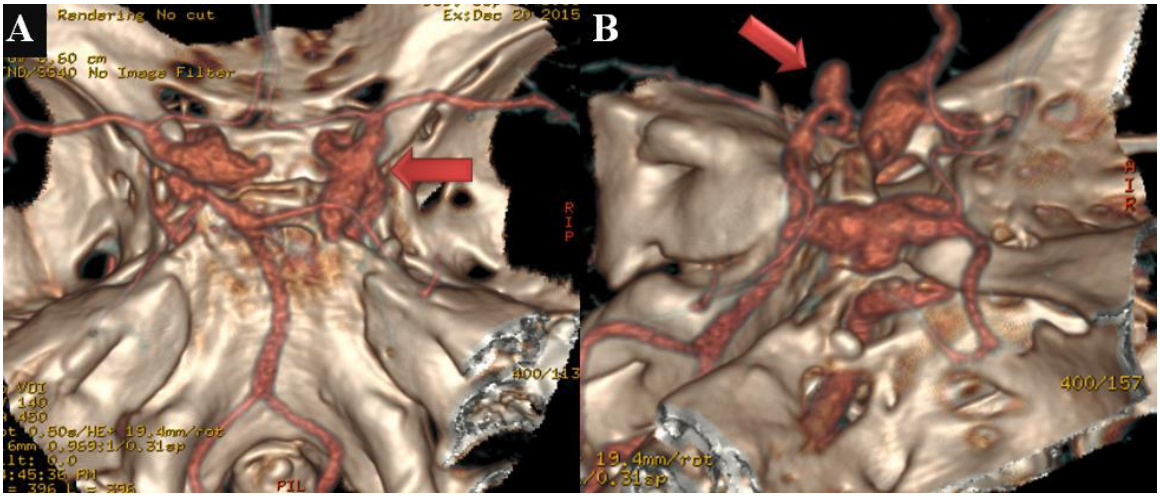


**Figure 138.** CT angiography with 3-dimensional reconstruction of the intracranial vessels showing dysplasia with right posterior communicating artery aneurysm (red arrow) (A). P1-P2 junction aneurysm (left posterior cerebral artery) (red arrow) (B) (from *Turliuc et al., 2017b*)

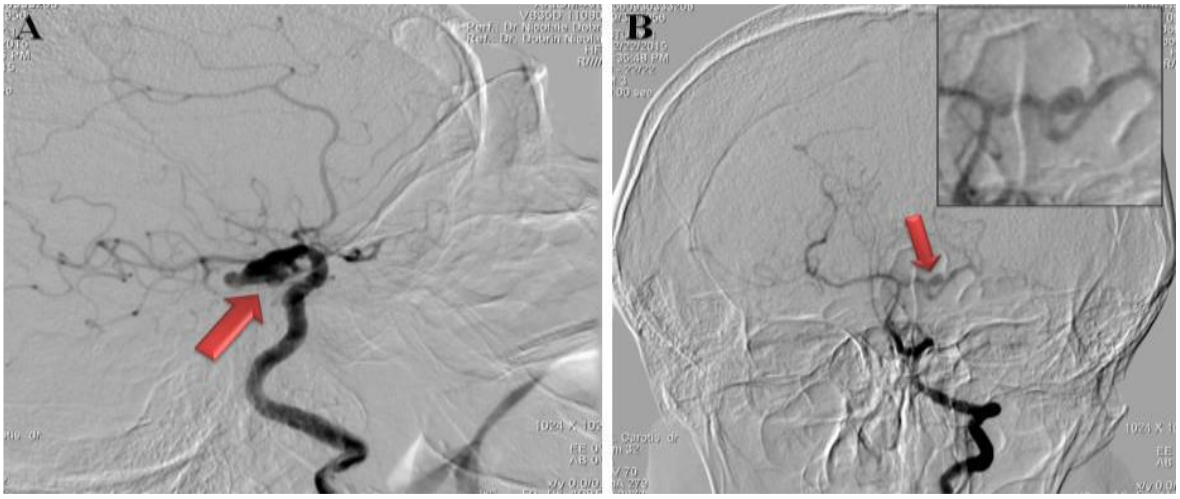


**Figure 139**. Cerebral angiography: lateral right view with vascular dysplasia (red arrow) (A). Left vertebral artery view with P1-P2 junction aneurysm from left posterior cerebral artery (B) *Courtesy of Dr. N. Dobrin* (from *Turliuc et al., 2017b*)

Pascual-Castroviejo was the first one to prove the relation between infantile hemangiomas and malformations of the cerebral and cervical arteries, the syndrome being called *cutaneous hemangioma-vascular complex syndrome* (*Pascual-Castroviejo, 1978, Turliuc et al., 2017b*).

Later, in 1996, Frieden *et al.* suggested the PHACE acronym to refer to the neurocutaneous syndrome: posterior fossa anomalies (P), hemangiomas of the face and scalp (H), arterial lesions (A), cardiovascular abnormalities (C) and eye's anomalies (E) (*Frieden et al., 1996*).

When supraumbilical raphe or sternal cleft are associated with the syndrome, the acronym becomes PHACES (*Cannady et al., 2006*). The clear criteria of the PHACE syndrome were later set by the American Academy of Pediatrics in 2009 (Table 39).

**Table 39**. Major and minor criteria for PHACE syndrome diagnosis (from *Metry et al., 2008*)

| ORGAN SYSTEM | MAJOR CRITERIA | MINOR CRITERIA |
|---|---|---|
| **Cerebrovascular** | Anomaly of major cerebral arteries<br>▪ Dysplasia of the large cerebral arteries<br>▪ Arterial stenosis or occlusion with or without moyamoya collaterals<br>▪ Absence or moderate to severe hypoplasia of the large cerebral arteries<br>▪ Aberrant origin or course of the large cerebral arteries<br>▪ Persistent trigeminal artery<br>▪ Saccular aneurysms of any cerebral arteries | Persistent embryonic artery other than trigeminal artery<br>▪ Proatlantal intersegmental artery (types 1 and 2)<br>▪ Primitive hypoglossal artery<br>▪ Primitive otic artery |
| **Structural brain** | Posterior fossa anomaly<br>▪ Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia | Enhancing extra-axial lesion with features consistent with intracranial hemangioma<br>▪ Midline anomaly<br>▪ Neuronal migration disorder |
| **Cardiovascular** | Aortic arch anomaly<br>▪ Coarctation of aorta<br>▪ Aneurysm<br>▪ Aberrant origin of the subclavian artery with or without a vascular ring | Ventricular septal defect<br>▪ Right aortic arch (double aortic arch) |
| **Ocular** | Posterior segment abnormality<br>▪ Persistent fetal vasculature (persistent hyperplastic primary vitreous)<br>▪ Retinal vascular anomalies<br>▪ Morning Glory disc anomaly<br>▪ Optic nerve hypoplasia<br>▪ Peripapillary staphyloma<br>▪ Coloboma | Anterior segment abnormality<br>▪ Sclerocornea<br>▪ Cataract<br>▪ Coloboma<br>▪ Microphthalmia |
| **Ventral or midline** | Sternal Defect<br>▪ Sternal cleft<br>▪ Supraumbilical raphe<br>▪ Sternal defects | Hypopituitarism<br>▪ Ectopic thyroid |

According to these criteria, our patient fit into definitive PHACE syndrome, which required the occurrence of: facial hemangioma > 5 cm in diameter + 1 major criteria, with the following valid criteria: facial hemangioma > 5 cm in diameter and dysplasia of large cerebral arteries, associating two cerebral aneurysms.

As regards facial hemangioma in PHACE syndrome, research has established four primary facial segments: *segment 1* (fronto-temporal area), *segment 2* (the maxillary area respecting the nasomedial sulcus), *segment 3* (the chin, mandible and lower lip) and *segment 4* (the medial frontal skin, philtrum and nasal bridge) (*Haggstrom et al., 2006, Turliuc et al., 2017b*). In our patient, facial hemangioma developed in segments 2 and 3. Moreover, it seems there is a connection between the regional distribution of facial hemangioma and the localization of arterial cerebral lesions (*Heyer et al., 2008*).

The specificity of this case consists of its late onset, at the age of 59 years, by rupture of aneurysm of right posterior communicating artery and the occurrence of a single facial hemangioma and the absence of the other cerebral, cardiovascular, ocular or median line abnormalities. Early PHACE syndrome diagnosis is important for the prevention of possible complications associated with this syndrome (*Turliuc et al., 2017b*).

### I.5.3.2.1.2. Subarachnoid hemorrhage in a patient with a factor V Leiden thrombophilia: case report and literature review

The coexistence of cerebral aneurysm and cerebral vein thrombosis in the setting of acute subarachnoid hemorrhage is rare, and the management of this patient is extremely difficult (*Filippidis et al., 2009*).

We report the case of a 42-year-old male patient admitted to our Department of Neurosurgery of *Prof. Dr. Nicolae Oblu* Emergency Clinical Hospital Iasi for GCS = 5, mydriasis with preserved photomotor reflex, acute respiratory failure and vegetative disorder. The patient had a history of untreated hypertension, smoking and diagnosed thrombophilia of heterozygous factor V Leiden mutation with right ischemic stroke of internal carotid cerebral artery four years ago. The head CT scan revealed subarachnoid hemorrhage and acute hydrocephalus (Figure 140) for which external ventricular drainage was performed. The cerebral computed tomography angiography did not reveal right internal jugular vein in the jugular foramen, right transverse sinus and sigmoid and right internal carotid artery thrombosis (*Turliuc et al., 2013*).

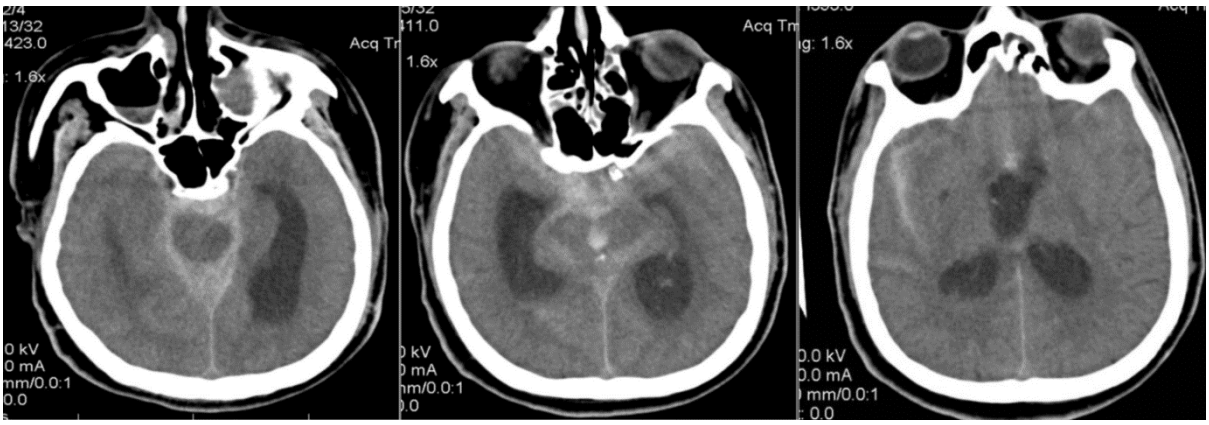

**Figure 140**. Head CT scan showing subarachnoid hemorrhage and acute hydrocephalus (from *Turliuc et al., 2013*)

The cerebral angiography showed left posterior communicating artery aneurysm (Figure 141) and complete occlusion of right internal carotid artery (Figure 142) with no anterograde flow across this occlusion (Figure 142). The endovascular treatment consisted of aneurysm occlusion with two spiral coils GDC-10 and one spiral Axium, which achieved a sufficient occlusion of the aneurysm (Figure 141).

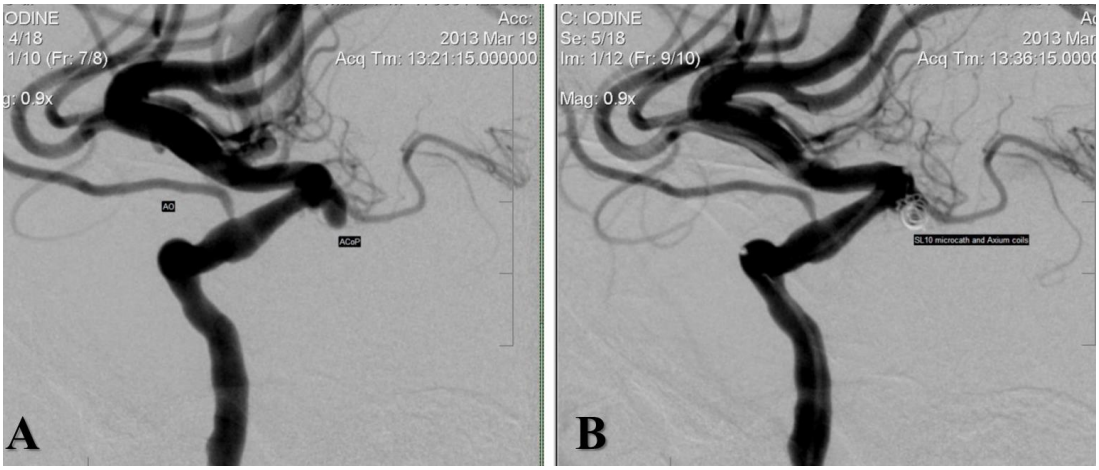


**Figure 141**. Cerebral angiography showing left posterior communicating artery aneurysm (A) and aneurysm occlusion with spiral coils (B). *Courtesy of Dr. N. Dobrin* (from *Turliuc et al., 2013*)

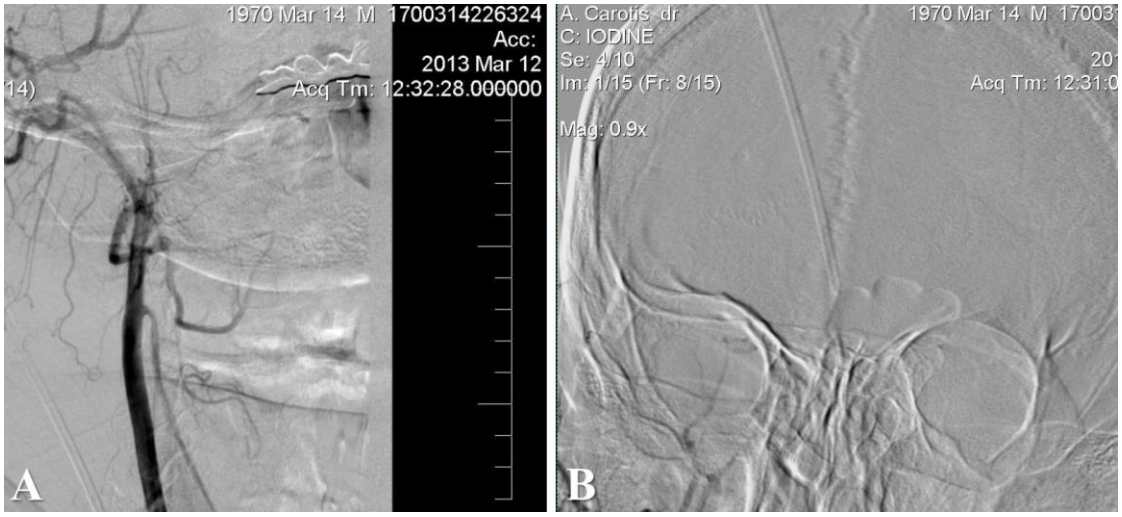


**Figure 142**. Cerebral angiography showing complete occlusion of right internal carotid artery (A) with no anterograde flow across this occlusion (B). *Courtesy of Dr. N. Dobrin* (from *Turliuc et al., 2013*)

Both cerebral venous sinus thrombosis and intracranial aneurysms are caused by subarachnoid hemorrhage (*Tufano et al., 2013*). In the first case, subarachnoid hemorrhage is distributed over the cortical surface of the brain, typically associated with cortical venous infarction. If the two entities coexist, it is vital to determine the first cause of subarachnoid hemorrhage and adequate treatment: aneurysm treatment or venous thrombosis treatment by anticoagulation (*Davagnanam and Brew, 2008*).

In our case, thrombophilia with a mutation of the factor V Leiden was a possible risk factor for the occurrence of venous sinus thrombosis, and this case-report clearly illustrates the difficulty of setting the etiological subarachnoid hemorrhage diagnosis. This coexists with a ruptured aneurysm in a patient known with factor V Leiden thrombophilia and cerebral vein thrombosis; although rare and dangerous, it is a curable disease. Endovascular coils embolization of the aneurysm and subsequent heparin anticoagulation in an attempt to prevent thrombus propagation, conducted to excellent results (*Turliuc et al., 2013*).

### I.5.4. Iconodiagnosis in neurosurgery and neuronal sciences

#### I.5.4.1. Iconodiagnosis research about the hydrocephalus of King Charles II of Spain

**Turliuc MD**, Cucu AI, Perciaccante A, Tosolini G, De Luca S, Costachescu B, Costea CF. *Hydrocephalus of King Charles II of Spain, the Bewitched King*. European Neurology 2019, 81(1-22):76-78. (Impact Factor in 2018 = 1.235)

In about 1685, the painter Juan Carreño de Miranda painted King Charles II of Spain. The picture showed a tall slender person with a bumpy forehead and protruding jaw. Based on the pictures painted during the king's rein, we have emitted a few clinical diagnosis suppositions, in an attempt to set an iconodiagnosis (*Turliuc et al., 2019a*).

Charles II of Spain (1661-1700) (Figure 143) was the last king of the Spanish Habsburg dynasty (*Turliuc et al., 2019a).* Throughout his life, Charles II suffered from a number of different disorders (*Bennassar, 2000, Gargantilla, 2005, Turliuc et al., 2019a, Kamen, 1983*) and is known as *El Hechizado*, whereas he was mentally retarded and physically disabled and disfigured (*Alvarez et al., 2009*). Later research has come to the conclusion that the predilection for endogamy of the Spanish branch of the Habsburg family induce to the segregation of this family from the neighboring communities and to the occurrence of consanguinity (*Alvarez et al., 2009, Ceballos and Alvarez, 2013, Turliuc et al., 2019a*).

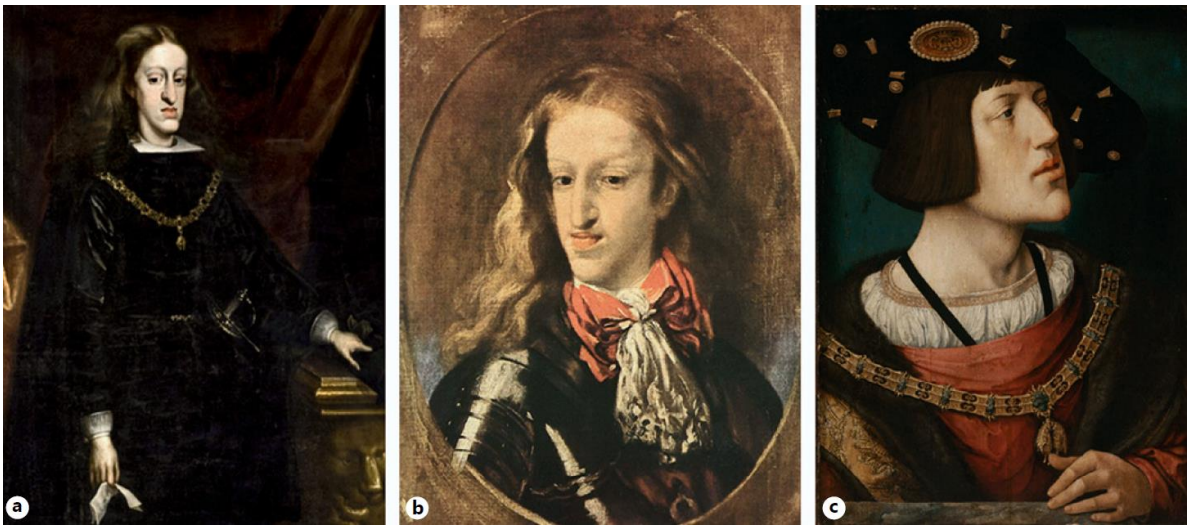


**Figure 143**. Charles II of Spain, *Juan Carreño de Miranda (c. 1685), Museum of Art History, Vienna* (a). King Charles II, *Claudio Coello (1675-1680), The Prado Museum, Madrid* (b). Portrait of Charles V, *Bernard van Orley (c.1515-1516), Museum of Fine Arts, Budapest* (c) (public domain) (from *Turliuc et al., 2019a*)

Charles could not speak until the age of 4 years and he could not walk until the age of 8-10 years (*Alvarez et al., 2009, Littell, 1849*), and *"his mind, too, was a constant prey to a corroding melancholy, which appears to have been in a great measure produced by the most ignoble and womanish superstitions"* (*Dunlop, 1834, Turliuc et al., 2019a*).

He was treated like a baby until he was 10 and left completely uneducated, for fear of overstraining a fragile child (*Littel, 1849*). The American historians Will and Ariel Durant described Charles II as *"short, lame, epileptic, senile and completely bald before 35, he was always on the verge of death, but repeatedly baffled Christendom by continuing to live"* (*Durant and Durant, 1963*). He eventually died in Madrid at the age of 38.

As concerns the efforts of determining the disease that Charles II suffered from, many contemporary authors have speculated on various diseases, most of them genetic, such as: fragile X syndrome (*Navalón Ramón and Ferrando Lucas, 2006*), Klinefelter syndrome (*Gargantilla, 2005*), pituitary hormone deficiency and renal tubular acidosis (*Alvarez et al., 2009*), or male XX hermaphroditism with a fragile X syndrome (*Garcia-Escudero López et al., 2009*).

Regardless of the king's disease, considering his signals and symptoms like macrocephaly, mental retardation and late growth, as well as his vomiting and epileptic seizures in his childhood, in our opinion they were related to hydrocephalus (*Turliuc et al., 2019a*).

Necropsies were not usually performed on kings, but since Charles II was considered to be bewitched, a post-mortem examination was conducted, the conclusions of which were that he *"did not contain a single drop of blood; his heart was the size of peppercorn; his lungs corroded; his intestines rotten and gangrenous; he had a single testicle, black as coal, and his head was full of water"* (*Gargantilla, 2005, de Moragas, 1970*). Although there are is no clear evidence that could support our etiological assumption related to Charles II's hydrocephalus, we may however argue that herpetic infection, which he was believed to have suffered from after his birth, may have caused it, as herpetic infections are known to cause hydrocephalus (*Hayashi et al., 1986, Takano et al., 1995*).

### I.1.5.4.2. Iconodiagnosis research on spinal neurosurgical and neurological pathology in biblical descriptions

As an exercise in iconodiagnosis, I focused on the main descriptions in the Holy Bible of several diseases of the spine, in an attempt to identify the most common neurosurgical spine pathologies in Jews during biblical times.

Turliuc S, Costea CF, Cucu AI, Dumitrescu AM, Dumitrescu GF, **Turliuc DM**. *Biblical descriptions of spinal neurological and neurosurgical pathology.* Romanian Neurosurgery 2016, 30(3):360-365.

The Bible contains several descriptions of spinal disease, which were depicted in famous paintings along the centuries. Although in neighboring Egypt there were medical schools as early as the 15$^{th}$ century BC, during biblical times, the Israelites did not have a medical system in place, the priests playing the role of doctors (*Hastings, 2004*). They conducted their healthcare duties according to the theories of Leviticus, a moral code and a public health and preventive medicine treaty.

The priests of the biblical period had knowledge about infectious diseases, they knew how to recognize, observe and isolate it in time. Therefore, due to these *health laws*, compared to other countries, Israel was considered a fairly healthy country (*Hastings, 2004*).

We would like to focus on two cases of the multitude of spinal disorders described in the Holy Bible, which we analyzed and published in a review (*Turliuc et al., 2016i*).

A common affliction of ancient Israelites was tuberculosis, which could also be located at the spinal level, producing spinal kyphosis and which in the main refers to Pott's disease. About this condition, Hebrew priests knew that it was contagious (*Bromiley, 1995*). One case described in the Bible by Luke, who was also a doctor, is that of an elderly woman, who had been hunched for 18 years (Figure 144). Since the disease had been long-lasting and had produced spinal kyphosis, it could have been either a chronic infectious disease such as tuberculosis or ankylopoietic spondylitis, or a degenerative disease of the spine, fractures or osteoporosis (*Turliuc et al., 2016i*).

Another case described in the Gospel of John is that of a paraplegic healed by Jesus. Considering that the patient had had a motor deficit for so long, he probably suffered most likely from amyotrophic lateral sclerosis (*Bromiley, 1995*), because the Bible tells us that the man could move with the help of crutches, as it can be seen in the picture (Figure 144).

In conclusion, the vast majority of medical cases presented in the Holy Scriptures are short and have a mystical glow, which makes it impossible to set the clear diagnosis of the disease (*Turliuc et al., 2016i*).

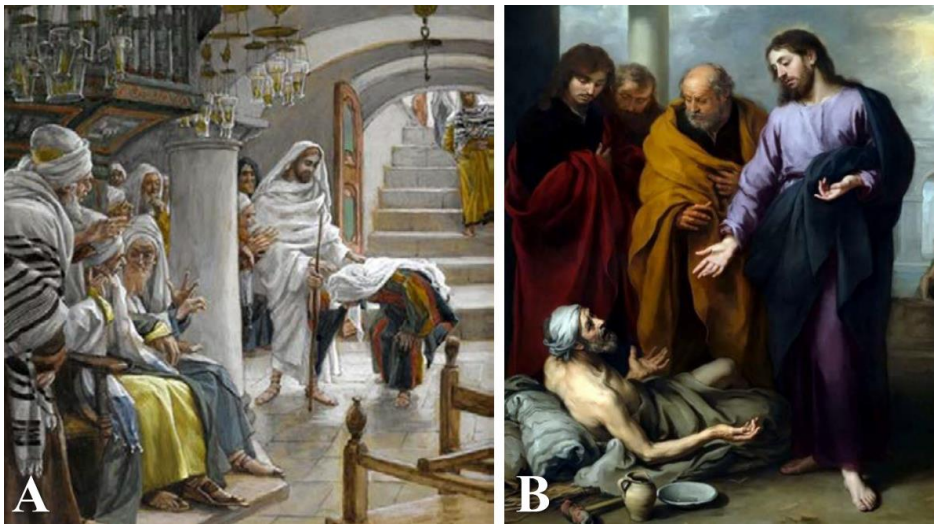


**Figure 144**. The woman who had an infirmity (c.1886-1896), *James Tissot, Brooklyn Museum, New York* (A). Christ healing the paralytic at the pool of Bethesda (c.1667), *Bartolome Esteban Murillo, The National Gallery, London* (B). (public domain) (from *Turliuc et al., 2016i*)

### I.5.4.3. Iconodiagnosis research on Chinese medical portraits depicting the late stage of a female with breast cancer

Perciaccante A, Cucu AI, Coralli A, **Turliuc MD**, Costea CF, Bianucci R. *Mid-19th century Chinese medical portraits depict late-stage female breast tumors*. Lancet Oncology 2019, 20(10):1347-1348. (Impact Factor in 2018 = 35.386)

We reported one of the biggest pictorial mid-19$^{th}$ century collections of breast tumors depicted by the painter Kwan Kiu Cheong (Lam Qua) (1801-1860) (**Yale University. Peter Parker's Lam Qua paintings collection, Perciaccante et al., 2019*).

Between 1836 and 1855, he painted several medical portraits of patients of physician Peter

Parker (1804-1888), a founder of the first Western-design hospital in China, the Ophthalmic Hospital in Canton (*Perciaccante et al., 2019, Chan et al., 2011*).

Doctor Parker commissioned Kwan Kiu Cheong to paint preoperative portraits of ill people who had large neoplasia or other important abnormality and who came to his hospital for treatment. Among these at least 115 oil paintings (*Gilman, 1986*), there is an impressive collection of 80 paintings held by the Harvey Cushing/John Hay Whitney Medical Library at Yale University (**Yale University. Peter Parker's Lam Qua paintings collection*)

We analyzed these 80 de paintings and noted that 37% (*n=11*) were late-stage breast tumors of Chinese women. Macroscopic morphological observation enabled us to conclude that the Chinese painter recorded one of the earliest depictions of Paget's disease of the breast (*Karakas, 2011*). Portrait no. 24 shows few signs specific of this type of cancer: eczema-like rash in the nipple area and adjacent areolar skin, ulceration and nipple inversion (*Perciaccante et al., 2019*) (Figure 145).

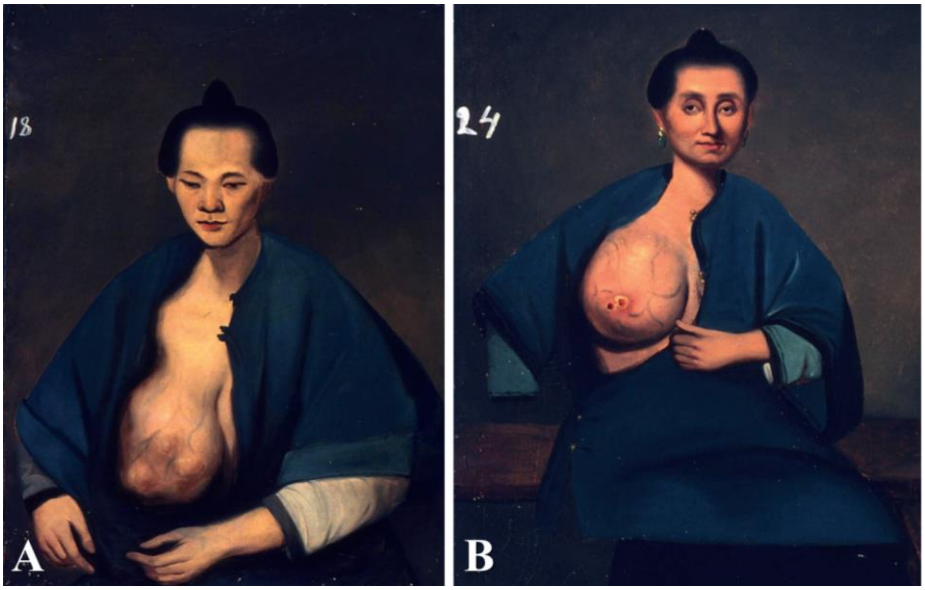


**Figure 145**. Portrait number 18. Description: woman seated. A large, malignant tumor is evident on her right breast, (1830-1850) (A). Portrait number 24 shows a possible case of Paget's disease of the breast (1830-1850) (B), Yale University, Harvey Cushing/John Hay Whitney Medical Library (from *Perciaccante et al., 2019*)

Based on the identified lesions, we may conclude that the patients came to Parker's hospital in late stages of the illness, and the reason may lie in the cultural and historical background of mid-19th century China: despite the presence of hospitals run by Imperial Court, patients preferred to be managed at home by family members (*Kang, 2012, Perciaccante et al., 2019*).

The entire collection provides indirect information about breast cancer epidemiology in mid-19th century China. Furthermore, the International Association of Cancer Registries reported that the most common neoplasia in Chinese women is breast neoplasia, with an incidence of 21.6 cases per 100.000 (*Fan et al., 2014, Bray et al., 2018, Perciaccante et al., 2019*).

Also, the Chinese National Central Cancer Registry demonstrated, in 2008 that breast neoplasia is the most common type of cancer among women in urban areas and the fourth most common in rural regions *(* IACR, Fan et al., 2014, Perciaccante et al., 2019*).

Also, in Guangzhou, the same area where Kwan Kiu Cheong's patients came from, in 2012, an age rate of 46.6 cases per 100.000 women was reported (*Fan et al., 2014*). Newer studies from 2018 (*Bray et al., 2018, Perciaccante et al., 2019*) further confirm the increase in breast cancer incidence in Chinese women.

### I.5.5. Research of the popes' contribution to the development of anatomy and medical-surgical sciences in European universities

Cucu AI, Costea CF, Perciaccante A, Turliuc S, Ciocoiu M, **Turliuc MD**. *The Anatomy of Papal Tiara: A Story About Popes' Contribution and Protection of Anatomists*. Journal of Religion and Health 2019, 58(4):1307-1327. (Impact Factor in 2018 = 1.235)

With the beginning of the 13th century, the popes played a very important and undeniable role in the evolution and advancement of anatomy and medical-surgical sciences in the universities of Europe, through the support and protection they offered to the anatomists of the time, who were also, in most cases, the popes' personal doctors (*Cucu et al., 2019d*).

Thus, the popes constantly sought the most scientific medical men of their day to be their personal physicians (*Walsh, 1915*), choosing the best doctors and the most brilliant anatomists of superior schools of the Papal States, universities that were under ecclesiastical tutelage of the Pope (*Cucu et al., 2019d*).

During Pope Innocent III's pontificate (Figure 146), the first papal doctor was appointed, whom he called *medicus pape*. Historical sources disagree on this point, as some say it was the Italian physician Giovanni Castellomata (*Paravicini-Baglani, 2000*), while others point to Guy of Montpelier (1160-1208) (Figure 146) (*Walsh, 1915*).

Pope Gregory IX (c. 1145 or 1170-1241) (Figure 146) followed the pattern as Pope Innocent III and appointed Ricardus Anglicus (1180-1252) as his personal doctor. He was famous for several medical writings, including Micrologus, a short medical encyclopedia (*Sarton, 1927-1948*). He was Pope Gregory IX's personal physician from 1227 until his death in 1241, after which he returned to Paris.

Pope John XXI (c. 1205 or 1220-1277) (Figure 146) was the only physician and pope at the same time that the Catholic Church has ever had (*McBrien, 1997*). Being in his turn Pope Gregory X's personal physician, Pope John XXI wrote an ophthalmology treatise*, Liber de Oculo*, as well as other important medical treatises like *Thesaurus Pauperum* (Figure 146), *Summa medicinae* and *Liber de conservanda sanitate* (*Blanchard, 1995, Prioreschi, 2003*).

While painting the Sistine Chapel, Michelangelo (Figure 146) injured himself many times and he used Pope John XXI's prescription: when something falls into the eyes, make a wash with honey, rose water and also milk (*Blanchard, 1995, Cucu et al., 2019d*).).


**Figure 146**. "Pope Innocent III, *Monastery of St. Benedict, Italy* (A). Guy of Montpellier (B). Pope Gregory IX approving the Decretals, *fresco by Raffaello Sanzio (1510–1511), Palazzi Pontifici, Vatican* (C). Pope John XXI (D). Thesaurus pauperum (first page) (c. 1500), *Bartolomeo de'Libri, Florence* (E). Michelangelo Buonarroti by *Daniele da Volterra (c. 1544), Metropolitan Museum of Art, New York* (F)". (public domain) (from *Cucu et al., 2019d*)

When he was elected pope of the Catholic Church, Pope Honorius the Fourth (c. 1210-1287) (Figure 147) was already old and ill (he had gout). Throughout the last few years of his popedom, he was medically assisted by the well-known medical professor Taddeo Alderotti (c. 1210-1295) (*Napier, 1846*), the founder of the Medical School of Bologna (Figure 147).

Being concerned with the academic activity of universities in Europe, Pope Nicholas the Fourth (1227-1292) (Figure 147) was the official founder of the University of Montpellier, recognized with important papal bull Quia sapientia, which also incorporated medical schools (*Vergani et al., 2012, Cucu et al., 2019d*).). By means of these schools, Pope Nicholas the Fourth promoted the University of Montpellier to the level of *stadium generale* (university), conferring on his doctors *ius ubique docendi*, that is the right to teach in another university without previous assessment (*Janin, 2008, Cucu et al., 2019d*).). Simon Januensis (1288-1303) was his physician and also a botanist and subdeacon, being the author of the first essential dictionary of medicine called *Synonyma Medicinae* (*Clavis Sanationis)* (*Gutiérrez Rodilla, 2004, Cucu et al., 2019d*).).

Pope Urban V (1310-1370) (Figure 147) helped the renowned Guy de Chauliac (Figure 147), who was always requested by popes for his services (*Cucu et al., 2019d*, *Walsh, 1915).* He returned his favors and expressed a constant interest for the medical division of the University of Montpellier (*Walsh, 1915*), and also for allowing him to autopsy and analyze bodies infected with plague (*Para, 2016*).

Pope Sixtus the Fourth (1471-1484) (Figure 147), known for his important achievements, the Vatican Library and the Sistine Chapel (*Pacifici, 1921*), is known for his main contribution to the advancement of anatomy. He gave a permissive Papal Bull for the University of Tübingen, which

permitted for necropsies, but with confirmation, approval and blessing of local bishops (*Nuland, 1989, Weisz, 1997*).

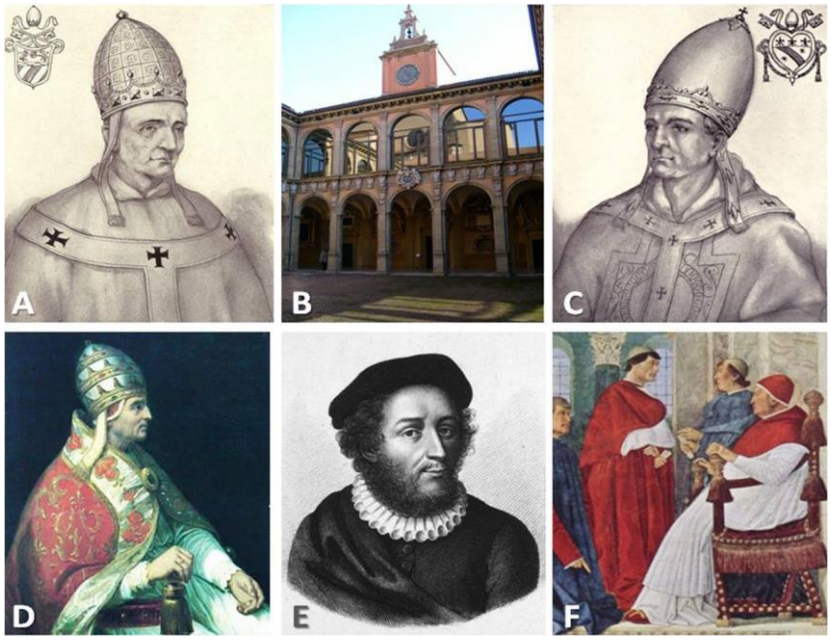


**Figure 147**. "Pope Honorius IV, *The lives and times of the popes (1911) by Artaud de Montor, New York. Reproduced from Effigies Pontificum Romanorum Dominici Basae* (A). Palazzo dell'Archiginnasio (the wing with the Anatomical theatre), *Bologna* (B). Pope Nicholas IV, *The lives and times of the popes (1911) by Artaud de Montor, New York. Reproduced from Effigies Pontificum Romanorum Dominici Basae* (C). Pope Urban V by *Calixte Serrur, Palace of Popes, Avignon* (D). Guy de Chauliac (1914) (E). Pope Sixtus IV appoints Bartolomeo Platina prefect of the Vatican Library (detail), *fresco by Melozzo da Forli (1477), Vatican Library* (F)". (public domain) (from *Cucu et al., 2019d*)

Pope Julius the Third (1487-1555) (Figure 148), recognized as the Pope with many physicians, funded the University of Rome, allowing only the Medical College to award grades in Medicine (*Cucu et al., 2019d*, *Gaudio and Memoli).*

Pope Paul IV (1476-1559) (Figure 148) had as his personal anatomist and physician Mateo Realdo Colombo, who represents, together with Eustachius and Vesalius, "the trinity of great original investigators in anatomy in mid-16$^{th}$ century" (*Walsh, 1915, Cucu et al., 2019d*).). Colombo dedicated his book *De re anatomica libri XV* (Figure 148) to Pope Paul the Fourth.

The renowned anatomist Costanzo Varolio was Pope Gregory XIII's (1502-1585) personal physician (Figure 148), whom he brought to Rome to instruct at the Sapienza University (*Westfall, 1995*).

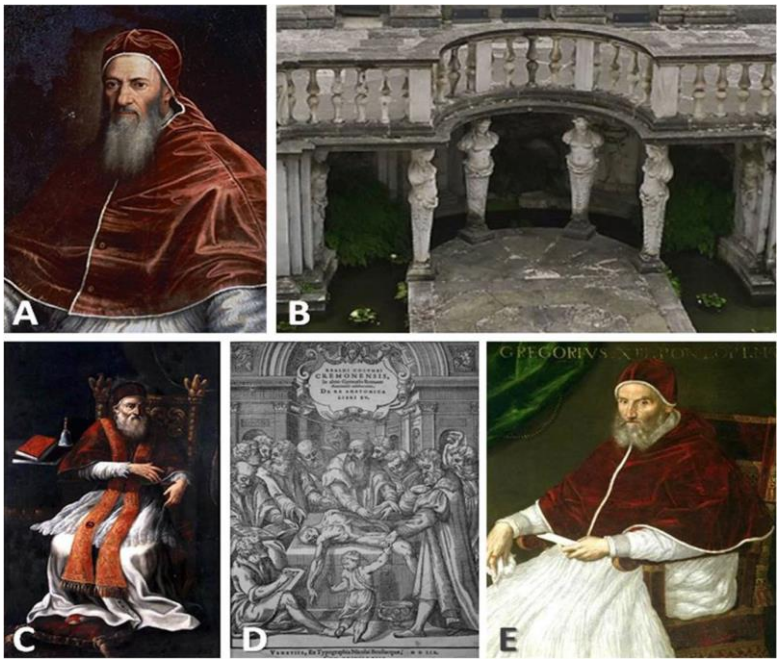


**Figure 148**. "Pope Julius III (A). Nymphaeum loggia (detail) *of the Villa Giulia, by Bartolomeo Ammannati, Rome* (B). Pope Paul IV (C). *De re anatomica libri XV* (title page), 1572 (D). Pope Gregory XIII (1502–1585), *three-quarter-length, seated, painting by Lavinia Fontana (c. 1600–1625)* (E)". (public domain) (from *Cucu et al., 2019d*)

Among other personal physicians of the popes we mention Andrea Cesalpino (1519-1603) (Figure 149), professor of medicine in Pisa, who was Pope Clement VIII's (1536-1605) physician (Figure 149), also known for having performed the necropsy of San Filippo Neri (*Bayon, 1939*) (Figure 149).


**Figure 149**. "Pope Clement VIII, by anonymous Italian, *Duesseldorfer Auktionshaus* (A). Election of Pope Clemens VIII in 1592 by *Louis de Caullery (1600), Petit Palais, Paris* (B).

Andrea Cesalpino, painting by *Battista Ricci, Rettorato Università di Pisa* (C). St. Filippo Neri in Ecstasy, painting by *Guido Reni (1614), Church Santa Maria in Vallicella, Rome* (D). Pope Innocent XI (1787) (E)". (public domain) (from *Cucu et al., 2019d*)

Marcello Malpighi (1628-1694) (Figure 150) was the friend and personal physician of Pope Innocent XII (1615-1700) (Figure 150). He was professor at the University of Bologna and Pisa (*Karamanou and Androutsos, 2010, Meli, 1997, Cucu et al., 2019d*).

After Malpighi's death, Pope Innocent XII accepted that the autopsy of his special friend and personal physician be performed in the basilica of Saints Vincent and Anastasius (Figure 150) by the most famous anatomists of the time: Giorgio Baglivi, Antonio Maria Valsalva and Giovanni Maria Lancisi (*Cunningham, 2016, Cucu et al., 2019d*).

Pope Clement XI (1649-1721) (Figure 150) chose as his personal physicians Giovanni M. Lancisi (*Black and Goldoni, 1828*) and Bellini Lorenzo (1643-1704), professor of medicine at the University of Padova, who was known for his studies about kidney structure.


**Figure 150**. "Pope Innocent XII (A). Marcello Malpighi, painting by *Carlo Cignani (1683), Accademia di belle arti di Bologna* (B). Saints Vincent and Anastasius Church near Fontana di Trevi (C). Festival before the Quirinale Palace, painting by *Antonio Cioci (1767), The State Hermitage Museum, Sankt Petersburg* (D). Pope Clement XI (E)". (public domain) (from *Cucu et al., 2019d*)

The popes played a critical and crucial role in the progress, evolution and advancement of anatomy and also medical-surgical sciences through aid, support and protection they offered to anatomists, who were in the vast majority of cases the popes' personal doctors, as well as through the integration of medical schools in the European universities (*Cucu et al., 2019d*).

# Section II. Directions for the development of scientific, professional, and academic activity

In view of the activity carried out so far, I am planning to continue handling some theorems previously approached, respectively brain tumor pathology and topics that concern pathology neighboring other surgical specialties. On a professional level, I am aiming to improve myself as much as possible regarding minimally invasive techniques. In regards to my teaching activity, I intend to introduce modern learning methods to both students and resident physicians. In the following, I will briefly present the outline for the development of my scientific, professional, and academic activity.

## II. 1. Scientific activity

Considering the areas of interest addressed in the postdoctoral period, the interdisciplinary collaboration that I have cultivated in all these years, and the preparation on niche areas, I will focus on the following fields of scientific research in the coming period:

### II.1.1. Functional neurosurgery

**Deep brain stimulation** of the cingulate gyrus is a minimally invasive surgical technique that is used as a last-resort treatment in psychiatric disorders refractory to psychiatric treatment. Given the wide range of psychiatric therapeutic possibilities and of strict criteria for inclusion, the number of patients receiving neurosurgical treatment is low. Broad studies are conducted for patients with obsessive compulsive disorder and less for patients with depression.

I will address the deep brain stimulation in patients diagnosed with depression as a study topic, because the prevalence of depression worldwide is > 300.000.000 , the recurrence rate after the first episode of relapse increases by 20%/year, and over 1/3 of the patients diagnosed with major depression become resistant to treatment, while these patients have the highest suicide rate.

Experimental and clinical studies that prove the long-term effect of antidepressants and prevent relapse stimulating nerve structures involved in the development of depression have developed since 2005. A clinical study from 2019 showed the efficacy of stimulating the cingulate gyrus in the treatment of major depression. Studies related to stimulation of other brain areas known to be involved in the mechanisms of depression (anterior limb of internal capsule, nucleus accumbens) are currently at the experimental stage (*Crowell et al., 2019*).

The study of deep brain stimulation in patients with major depression will involve problems of medical ethics and strict compliance with the selection criteria.

The study will enable teamwork, with very close collaboration between the neurosurgeon, psychiatrist, neurophysiologist, neuroradiologist, and psychologist.

The study will be possible due to my training in deep brain stimulation and neuronavigation techniques.

Considering the existing technical possibilities and the skills I acquired over the years, another topic of research would be the deep brain stimulation of the nervous structures involved in the appearance of the disorders of the extrapyramidal system.

### II.1.2. Brain trauma and hypothalamic-pituitary axis

Brain trauma represents the single leading cause of death in young patients. The hypothalamic-pituitary axis is often involved in severe brain injuries, which causes some problems strictly related to its structure, but also to its connections to other brain structures. The mechanism underlying these conditions has not been sufficiently known. There are several hypotheses related to metabolic and vascular changes in the brain, the response of brain tissue to hypoxia and to the stress associated with the critical state of the patient. A decade ago, endocrinological dysfunctions were thought to be due to severe and moderate brain injuries, but recent studies show that even minor brain trauma are involved in affecting the hypothalamic-pituitary axis and its connections to other brain structures.

Therefore, the diagnosis and treatment of these lesions are based solely on the experience of the clinician, they are not standardized which could be to the detriment of the patient. In this sense, it is necessary to develop a protocol for the diagnosis and treatment of the conditions determined by trauma caused to the hypothalamic-pituitary axis.

**A first study topic** would be the hydroelectrolytic disorders caused by posterior pituitary trauma, which would be represented by the onset of post-traumatic diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion. Hydroelectrolytic disorders can occur both by affecting the posterior pituitary, but also by corticotropic insufficiency and affecting the hypothalamic center of thirst. Potential clinical studies would concern the optimal neuroimaging exploration that can be performed for diagnosis and them moment when it should be performed to establish an effective treatment as soon as possible, and also the establishment of the necessary biological samples and the time when they should be collected for an early diagnosis and the rapid establishment of the appropriate treatment.

**A second study topic** would be related to the involvement of the hypothalamic-pituitary axis in the post-traumatic impairment of cognitive and vegetative functions and would aim for an early diagnosis and treatment of post-traumatic brain syndrome. This topic involves a long-term clinical evaluation of patients with severe brain trauma correlated with high-performance dynamic neuroimaging (MRI 3T, PET), and lastly, neurosurgical treatment by minimally invasive surgical technique.

## II.2. Professional activity

The development of professional skills is closely related to the scientific activity that I intend to conduct for the time being. For this reason, I aim to improve my minimally invasive surgery skills that I have acquired over the years. This involves improving the technique of deep brain stimulation, but also those of neuroendoscopy and of endoscopic transsphenoidal surgery.

Another objective of my professional activity will be to maintain the interdisciplinary relationships developed over time, but also to cooperate with new specialties, such as endocrinology.

**II. 3. Academic activity**

The first objective of my teaching activity is to optimize learning methods for both students and resident physicians. Thus, I propose the introduction of the medical scenarios and the virtual patient in the study of neurosurgical pathology, the introduction of the iconodiagnosis for the description of the clinical cases, and changing the teaching method from a one-way presentation to an interactive form of learning.

This can be done in collaboration with the Institute of Anatomy. Thus, one can resort to as many practical applications as possible by using the virtual anatomy program and carrying out virtual dissections at the level of the cephalic extremity, respectively at the level of the brain, but also at the spinal cord level. After establishing the simulation center, the next learning stage after virtual anatomy would be the development of surgical skills. These shall allow me to organize work-shops that would be the basis for organizing hands-on work-shops, extremely important activities in training young neurosurgeons.

My mission as a teacher is help both students and resident physicians develop not only surgical skills, but also skills concerning medical communication and scientific research. In this sense, I intend to conduct together with them case presentations, clinical studies, to elaborate scientific articles and presentations for scientific events.

**II.4. Conclusion**

This habilitation thesis is a presentation of my entire career, of my scientific, professional, and academic achievements, activity on which my future evolution is based scientifically, professionally and academically. Based on the experience already gained, I will continue to further existing scientific topics, will approach new scientific research topics, and will try to make medical education more efficient in the field of neurosurgery.

# Section III - References

*American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, 2013.

*CENTER-TBI, https://www.center-tbi.eu/publications

*EFSA, Scientific opinion on the substantiation of health claims related to the sugar replacers xylitol, D-tagatose, xylitol, sorbitol, mannitol, maltitol, lactitol, isomalt, erythritol, D-tagatose, isomaltulose, sucralose and polydextrose and maintenance of tooth mineralization by decreasing tooth demineralisation. *EFSA Journal* 2011, 9(4): 2076.

*IACR, International Association of Cancer Registries http://www.iacr.com.fr/index.php?option=com_content&view=article&id=101&Itemid=578

*UNSCEAR, Sources and effects of ionizing radiation: 2000 report to the general assembly, with scientific annexes, vol. II: Effects. United Nations, New York, 2000.

*UNSCEAR, Sources, effects and risks of ionizing radiation: Geneva (Switzerland): United Nations scientific committee on the effects of atomic radiation, 1988.

*UNICEF, The human consequences of the Chernobyl nuclear accident-a strategy for recovery. Geneva (Switzerland): United Nations development programme and UNICEF, 2002

*UNDP & UNICEF, The human consequences of the Chernobyl nuclear accident-a strategy for recovery. Geneva (Switzerland): United Nations development programme and UNICEF, 2002

*WHO Model Lists of Essential Medicines, 2015. http://www.who.int/medicines/publications/essentialmedicines/en/

*Yale University. Peter Parker's Lam Qua paintings collection. In: Harvey Cushing/John Hay Whitney Medical Library. Available on: http://whitney.med.yale.edu/gsdl/collect/ppdcdot/

1. Abbott E. *A History of Celibacy*. Cambridge: The Lutterworth Press, 2001.
2. Aboud E, Al-Mefty O, Yasargil MG. New laboratory model for neurosurgical training that simulates live surgery. *J Neurosurg* 2002, 97:1367-1372.
3. Abderhalden R. *Internal secretion*. Bombay: CIBA Monographs, 1951.
4. Abe T, Sato K, Otsuka T, et al. Optic Nerve decompression for orbitofrontal fibrous dysplasia. *Skull Base* 2002, 12:145-152.
5. Achrol AS, Rennert RC, Anders C, et al. Brain metastases. Nat Rev Dis Primers 2019, 5:1-26.
6. Adam A, Boyd J, Da Ponte LL. *Roman Antiquities: Or an Account of the Manners and Customs of the Romans: Designed to Illustrate the Latin Classics, by Explaining Words and Phrases, from the Rites and Customs to Which They Refer*. 8th Ed. New York: W. E. Dean, 1842.
7. Adamczyk M, Bulski T, Sowińska J, et al. Trigeminal nerve: artery contact in people without trigeminal neuralgia-MR study. Med Sci Monit 2007, 13:38-43.
8. Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg* 2018, 130(3):804-811.
9. Al-Holou WN, Yew AY, Boomsaad ZE, et al. Prevalence and natural history of arachnoid cysts in children. Clinical article. *J Neurosurg Pediatr* 2010, 5:578-585.
10. Al-Nuaimy WMT, Jalal JA, Mohammed BB. Ki-67 (MIB-1) and progesterone receptor in meningioma: an immunohistochemical study. *Iraqi Postgrad Med* J 2012, 11(2):157-167.
11. Al-Rodhan NR, Laws ER Jr. Meningioma: a historical study of the tumor and its surgical management. *Neurosurgery* 1990, 26: 832-846, discussion 846-847.
12. Albayram S, Adaletli I, Selcuk H, et al. Breast cancer metastasis involving pterygopalatine fossa: a cause of trigeminal neuralgia. *Headache* 2004, 44(9):927-928.
13. Albert DM, Rubenstein RA, Scheie HG. Tumor metastasis to the eye. I. Incidence in 213 adult patients with generalized malignancy. *Am J Ophthalmol* 1967, 63(4):723-726.
14. Ali MA, Carroll KT, Rennert RC, et al. Stereotactic laser ablation as treatment for brain metastases that recur after stereotactic radiosurgery: a multiinstitutional experience. *Neurosurg Focus* 2016, 41, E11.
15. Alpers BJ, Harrow R. Cranial hyperostosis associated with overlying fibroblastoma. *Arch Neurol Psychiatr* 1932, 28:339-356.
16. Alvarez XA, Figueroa J, Muresanu D. Peptidergic drugs for the treatment of traumatic brain injury. *Fut Neurol* 2013, 8:175-192.
17. Alvarez G, Ceballos FC, Quinteiro C. The role of inbreeding in the extinction of a European royal dynasty. *PLoS One* 2009, 4(4):e5174.
18. Alvarez XA, Sampedro C, Figueroa J, et al. Reduction in qEEG slowing over and after treatment with Cerebrolysin in patients with moderate-sever traumatic brain injury. *J Neural Transm* 2008, 115:683-692.

19. Alvarez AX, Sampedro C, Perez P, et al. Positive effects of Cerebrolysin on electroencephalogram slowing, cognition and clinical outcome in patients with postacute traumatic brain injury: an exploratory study. *Int Clin Psychopharmacol* 2003, 18:271-278.
20. Amatya VJ, Takeshima Y, Sugiyama K,et al. Immunohistochemical study of Ki-67 (MIB-1), p53 protein, p21WAF1, and p27KIP1 expression in benign, atypical, and anaplastic meningiomas. *Hum Pathol* 2001, 32(9):970–975.
21. Angulo JC, García-Díez M. Male genital representation in paleolithic art: erection and circumcision before history. *Urology* 2009, 74:10-14.
22. Antisdel JL, Janney CG, Long JP, Sindwani R. Hemostatic agent microporous polysaccharide hemospheres (MPH) does not affect healing or intact sinus mucosa. Laryngoscope 2008, 118(7):1265-1269.
23. Antoniu G (ed). *Explicații preliminare ale noului Cod Penal. Art. 182*, Vol.II, Bucuresti: Universul Juridic, 2011.
24. Aragão RE, Barreira IM, Gomes LM, et al. Choroidal metastasis as the first sign of bronchioloalveolar lung cancer: case report. *Arq Bras Oftalmol* 2013, 76(4):250-252.
25. Araghi HM, Haery C. Fibrous-osseous lesions of craniofacial bones. The role of imaging. *Radiol Clin North Am* 1993, 31:121-134.
26. Arevalo JF, Fernandez CF, Garcia RA. Optical coherence tomography characteristics of choroidal metastasis. *Ophthalmology* 2005, 112(9):1612-1619.
27. Arnold, F, Bemerkungen über den Bau des Hirns und Rückenmarks nebstBeiträgen zur Physiologie des zehnten und eilften Hirnnerven mehrern kritis-chen Mittheilungen so wie verschiedenen pathologischen und anatomischenBeobachtungen. Zürich: S. Höhr, 1838.
28. Arráez-Aybar LA, Bueno-López JL, Raio N. Toledo School of Translators and their influence on anatomical terminology. *Ann Anat* 2015, 198:21-33.
29. Arráez-Aybar LA, Sánchez-Montesinos I, Mirapeix RM, et al. Relevance of human anatomy in daily clinical practice. *Ann Anat* 2010, 192(6):341-348.
30. Arslan O. *Neuroanatomical Basis of Clinical Neurology*. Boca Raton: CRC Press Taylor and Francis Group, 2014.
31. Arslan M, Eseoğlu M, Güdü BO, et al. Transorbital orbitocranial penetrating injury caused by a metal bar. *J Neurosci Rural Pract* 2012, 3:178-181.
32. Asteriou C, Konstantinou D, Kleontas A, et al. Blurred vision due to choroidal metastasis as the first manifestation of lung cancer: a case report. *World J Surg Oncol* 2010, 8:2.
33. Baechli H, Gratzl O. Microvascular decompression in trigeminal neuralgia with no vascular compression. *Eur Surg Res* 2007, 39:51-57.
34. Bagshaw HP, Burt LM, Jensen RL, et al. Adjuvant radiotherapy for atypical meningiomas. *J Neurosurg* 2017, 126:1822-1828.
35. Balch CM, Oreskovich MR, Dyrbye LN, et al. Personal consequences of malpractice lawsuits on American surgeons. *J Am Coll Surg* 2011a, 213:657-667.

36. Balch CM, Shanafelt TD, Sloan JA, et al. Distress and career satisfaction among 14 surgical specialties, comparing academic and private practice settings. *Ann Surg* 2011b, 254:558-568.
37. Balch CM, Shanafelt TD, Sloan J, et al. Burnout and career satisfaction among surgical oncologists compared with other surgical specialties. *Ann Surg Oncol* 2011c, 18:16-25.
38. Barandiarán I, Oliver BM, del Rincón Martínez Á, González JLM. *Prehistoria de la Península Ibérica*. Barcelona: Ariel, 1999.
39. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004, 22, 2865-2872.
40. Barthélemy E, Loewenstern J, Konuthula N, et al. Primary management of atypical meningioma: treatment patterns and survival outcomes by patient age. *J Cancer Res Clin Oncol* 2018, 144(5):969-978.
41. Barthélemy EJ, Sarkiss CA, Lee J, Shrivastava RK. The historical origin of the term "meningioma" and the rise of nationalistic neurosurgery. *J Neurosurg* 2016, 125:1283-1290.
42. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 1996, 111: 209-219.
43. Bayon HP. Allusions to a "Circulation" of blood in MSS anterior to De motu cordis 1628. *Proceedings of the Royal Society of Medicine* 1939, *32:*707-718.
44. Beck DW, Menezes AH. Lesions in Meckel's cave: variable presentation and pathology. *J Neurosurg* 1987, 67(5):684-689.
45. Becker M, Kohler R, Vargas MI, et al. Pathology of the trigeminal nerve. *Neuroimaging Clin N Am* 2008, 18:283-307.
46. Bell C. *The Anatomy of the Brain: Explained in a Series of Engravings.* London: T. N. Longman & O. Rees. 1802.
47. Bennassar B. *La España de los Austrias* (1516-1700). Barcelona: Crıtica, 2000.
48. Berhouma M, Dubourg J, Messerer M. Cruveilhier's legacy to skull base surgery: premise of an evidence-based neuropathology in the 19th century. *Clin Neurol Neurosurg* 2013, 115:702-707.
49. Bernardo A. Establishment of next-generation neurosurgery research and training laboratory with integrated human performance monitoring. *World Neurosurg* 2017, 106:991-1000.
50. Better OS, Rubinstein I, Winaver JM, Knochel JP. Mannitol therapy revisited (1940-1997). *Kidney Int* 1997, 52:886-894.
51. Bikmaz K, Mrak R, Al-Mefty O. Management of bone invasive, hyperostotic sphenoid wing meningiomas. *J Neurosurg* 2007, 107:905-912.
52. Biondo-Simoes Mde L, Petrauskas R, Dobrowolski AG, et al. Validity of microporous polysaccharide hemispheres as a hemostatic agent in hepatic injuries: an experimental study in rats. *Acta Cir Bras* 2007, 22(Suppl. 1):29-33.
53. Bishop M, Shoemaker WC, Avakian S, et al. Evaluation of a comprehensive algorithm for blunt and penetrating thoracic and abdominal trauma. *Am Surg* 1991, 57(12):737-746.

54. Björses K, Holst J. Topical haemostatics in renal trauma-an evaluation of four different substances in an experimental setting. *J Trauma* 2009, 66:602-611.
55. Black PM. Harvey Cushing at the Peter Bent Brigham Hospital. *Neurosurgery* 1999, 45:990-1001.
56. Black J, Goldoni C. *Memoirs of Goldoni* (Vol. 1). London: Hunt and Clarke, 1828.
57. Blanchard D. Pope John XXI, ophthalmologist. *Documenta Ophthalmologica* 1995, 89: 75–84.
58. Boivie J. The termination in the thalamus and the zona incerta of fibres from the dorsal column nuclei (DCN) in the cat. An experimental study with silver impregnation methods. *Brain Res* 1971, 28:459-490.
59. Bonnal J, Thibaut A, Brotchi J, Born J. Invading meningiomas of the sphenoid ridge. *J Neurosurg* 1980, 53: 587-599.
60. Bratton SL, Chestnut RM, Ghajar J, *et al.* Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma* 2007, 24 Suppl 1:S14-20.
61. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA *Cancer J Clin* 2018, 68(6):394-424.
62. Bride BE, Robinson MM, Yegidis B, Figley CR. Development and validation of the Secondary Traumatic Stress Scale. *Research on Social Work Practice* 2004, 13, 490-502.
63. BriggsW. A new theory of vision. *Philos Trans R Soc Lond A* 1809, 2:540-542.
64. Brisman R. Gamma knife surgery with dose of 75-75.8 for trigeminal neuralgia. *J Neurosurg* 2004, 100(5):848-854.
65. Brisman R. *Retrogasserian ganglion glycerol injection with or without radiofrequency electro coagulation for trigeminal neuralgia*. In: Brisman R. (ed) *Neurosurgical and medical management of Pain*. Norwell: Kluwer Academic Publishers, 1989.
66. Bromiley GW. *International Standard Bible Encyclopedia*. Grand Rapids: Wm. B. Eerdmans Publishing, 1995.
67. Brothwell M, Brothwell D. Evidence for ancient meningiomas and a probable case from Medieval Tarbat, Scotland. *Int J Paleopathol* 2016, 13:65-69.
68. Bruckner BA, Blau LN, Rodriguez L, et al. Microporous polysaccharide hemosphere absorbable hemostat use in cardiothoracic surgical procedures. *J Cardiothorac Surg* 2014, 9:134.
69. Buck AH, Stedman TL. *A Reference Handbook of the Medical Sciences, Embracing the Entire Range of Scientific and Practical Medicine and Allied Science*. Vol. 4. New York: William Wood & Company, 1914.
70. Budohoski KP, Clerkin J, Millward CP, et al. Predictors of early progression of surgically treated atypical meningiomas. *Acta Neurochir (Wien)* 2018, 160(9):1813-1822.
71. Bulleid LS, James Z, Lammie A, et al. The effect of the revised WHO classification on the incidence of grade II meningioma. *Br J Neurosurg* 2019, 9:1-3. [Epub ahead of print]

72. Bulsara KR, Al-Mefly O, Shricve DC, Angtuaco EJ. *Meningiomas*. In: Berger MS. Prados MD (eds). *Textbook of Neuro-Oncology*. Philadelphia: Elsevier Saunders, 2005. p. 335.
73. Burdach KF. *Vom Baue und Leben des Gehirns.* Leipzig, Dyk'sche Buchhdlung, Volume 3, 1826.
74. Burdach KF. *Vom Baue und Leben des Gehirns*. Leipzig: Dyk'sche Buchhdlung, Volume 2, 1822.
75. Burdach KF. *Vom Baue und Leben des Gehirns*. Leipzig: Dyk'sche Buchhdlung, Volume 1, 1819.
76. Burke AB, Collins MT, Boyce AM. Fibrous dysplasia of bone: craniofacial and dental implications. *Oral Dis* 2017, 23(6):697-708.
77. Butti G, Assietti R, Casalone R, et al. Multiple meningiomas: A clinical, surgical, and cytogenetic analysis. *Surg Neurol* 1989, 31:255-260.
78. Caine RM, Ter-Bagdasarian L. Early identification and management of critical incident stress. *Critical Care Nurse* 2003, 23:59-65.
79. Cannady SB, Kahn TA, Traboulsi EI, Koltai PJ. PHACE syndrome: report of a case with a glioma of the anterior skull base and ocular malformations. *Int J Pediatr Otorhinolaryngol* 2006, 70(3):561- 564.
80. Cappabianca P, Magro F. The lesson of anatomy. *Surg Neurol* 2009, 71:597-598.
81. Cappello F, Gerbino A, Zummo G. Giovanni Filippo Ingrassia: A five-hundred year-long lesson. *Clin Anat* 2010, 23:743-749.
82. Catani M, Sandrone S. *Brain Renaissance: From Vesalius to Modern Neuroscience.* New York: Oxford University Press, 2015.
83. Ceballos FC, Alvarez G. Royal dynasties as human inbreeding laboratories: the Habsburgs. *Heredity* 2013, 111(2):114-121.
84. Champeaux C, Houston D, Dunn L. Atypical meningioma. A study on recurrence and disease-specific survival. *Neurochirurgie* 2017, 63(4):273-281.
85. Chan CC, Liu MM, Tsai JC. The first western-style hospital in China. Arch Ophthalmol 2011, 129:791-797.
86. Chandwick J, Mann WN. *The medical works of Hippocrates*. London: Blackwell Scientific, 1950, p 264.
87. Chang SM, Parney IF, McDermott M, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. *J Neurosurg* 2003, 98(6):1175-1181.
88. Chen F, Cao X, Yu J et al. Quaternary ammonium groups modified starch microspheres for instant hemorrhage control. *Colloids and Surfaces B* 2017, 159(1):937-944.
89. Chen F, Cao X, Chen X et al. Calcium-modified microporous starch with potent hemostatic efficiency and excellent degradability for hemorrhage control. *J Mater Chem B* 2015, 3:4017-4026.
90. Chen CC, Wei ST, Tsaia SC, et al. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: double-blind, placebo-controlled, randomized study. *Br J Neurosurg* 2013, 27: 803-807.

91. Chen CF, Liu XF, Meng XZ, Jia HY. Comparative study of mannitol-induced acute kidney impairments in patients of different ages suffering from subarachnoid hemorrhage. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2007, 19(12):727-730.
92. Chen YR, Breidahl A, Chang CN. Optic nerve decompression in fibrous dysplasia: indications, efficacy and safety. *Plast Reconstr Surg* 1997, 99:22-30.
93. Choi YM, Kim TY, Yoon KJ, et al. A Comparative Study on MIB-1, AgNORs and PCNA Expressions in Astrocytic Tumors. *J Korean Neurosurg Soc* 1997, 26(4):476-485.
94. Chung SB, Kim CY, Park CK, et al. Falx meningiomas: surgical results and lessons learned from 68 cases. *J Korean Neurosurg Soc* 2007, 42:276-280.
95. Cinteza M, Pana B, Cochino E, et al. Prevalence and control of cardiovascular risk factors in Romania cardio-zone national study. *Maedica* 2007, 2(4):277-288.
96. Ciofu ML, Sulea D, Nicolau A, et al. Management of orbital tumors presenting as unilateral exophthalmos. *Romanian Journal of Oral Rehabilitation* 2017, 9(4):66-72.
97. Cleland L, Davies G, Llewellyn-Jones L. *Greek and Roman Dress from A to Z*. Abingdon: Routledge, 2007.
98. Clohessy S, Ehlers A. PTSD symptoms, response to intrusive memories and coping in ambulance service workers. *Br J Clin Psychol* 1999, 38:251-265.
99. Constantinescu B, Bugoi R, *Social adaptation in Romania to the Chernobyl accident*, In: Lonergan SC (ed). *Environmental change, adaptation, and security*. Dordrecht: Kluwer Academic Publishers, 1999.
100. Cook PJ, Lawrence BA, Ludwig J, Miller TR. The medical costs of gunshot injuries in the United States. *JAMA* 1999, 282(5):447-454.
101. Costan VV, Sava A, Carauleanu A, et al. Histopatological and clinical characteristics of surgically removed cavernous venous malformations (so-called cavernous hemangiomas) of the orbit. *Rev Chim (Bucharest)* 2019, 70:350-354.
102. Costea CF, Turliuc MD, Sava A, et al. Periocular basal cell carcinoma: demographic, clinical histological and immunohistochemical evaluation of a series of 39 cases. *Romanian Journal of Morphology and Embryology* 2019, 60(1):77-86.
103. Costea C, Turliuc S, Cucu A, et al. The "polymorphous" history of a polymorphous skull bone: the sphenoid. *Anat Sci Int* 2018, 93(1):14-22.
104. Costea CF, Turliuc S, Cucu AI, Turliuc MD. To be or not to be Wilbrand's knee? A question that is looking for an answer. *Child's Nervous System* 2018a, 34(11):2135.
105. Costea CF, Turliuc S, Buzduga C, et al. The history of optic chiasm from antiquity to the twentieth century. Child's Nervous System 2017, 33(11):1889-1898.
106. Costea CF, Turliuc D, Sava A, et al. Principles and guidelines involved in the management of surgical acquired anophthalmia patients. *Romanian Journal of Oral Rehabilitation* 2016, 8(1): 59-64.
107. Costea CF, Cucu AI, Dimitriu G, et al. Understanding the psychological impact in a clinical case of eye globe rupture with forensic implications. *Romanian Journal of Oral Rehabilitation* 2016a, 8(2): 61-67.

108. Costea CF, Cucu A, Costan VV, et al. Visual impairment in orbitofrontal and sphenoidal fibrous dysplasia associated with sphenoid sinus mucocele. *Journal of Clinical Research and Ophtalmology* 2015, 2(4):054-057
109. Costea CF, Sava A, Dumitrescu GF, et al. Forensic aspects of ocular trauma. *Aperito Journal of Ophthalmology* 2015a, 1 (2):1-5.
110. Costinescu V, Palade OD, Stegaru G, et al. Combined endo- and extracranial approach for the sinonasal tumors invading the anterior skull base. *Rev Med Chir Soc Med Nat Iasi* 2003, 107(3): 110-115.
111. Crocker J, Murray PG. *Molecular biology in cellular pathology*. Chichester: Wiley 2nd ed., 2003.
112. Crowell A, Riva-Posse P, Holtzheimer PE, et al., Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Am J Psychiatry* 2019, 176(11):949-956.
113. Cruveilhier J. *L'Anatomie pathologique du Corps humain.* Paris: J.B. Baillière, 1829.
114. Cuciureanu ID, Hînganu MV, Stătescu C, et al. Morphopathological particularities of cerebrovascular diseases for patients in the northeastern area of Romania. *Rom J Morphol Embryol* 2019, 60(1):227-232.
115. Cuciureanu DI, Statescu C, Sascau RA, et al. Particularities of using contrast agents in diagnosis of stroke. *Rev Chim (Bucharest)* 2019a, 70(2): 685-688.
116. Cucu AI, Costea CF, Perciaccante A, et al. The history of Arachne through historic descriptions of meningiomas with hyperostosis: from history to the present. *World Neurosurgery* 2019a, 128:37-46.
117. Cucu AI, Costea CF, Turliuc MD, et al. Anatomical localization of intracranial grade II meningiomas in North-Eastern Romania. Our 25-years experience. *Romanian Neurosurgery* 2019b, 33(3): 232-238.
118. Cucu AI, Costea CF, Turliuc MD, Dumitrescu GF, Sava A, Poeata I. Are there any correlations between demographic characteristics, tumor location and Ki-67 labeling index in intracranial atypical meningiomas (WHO grade II)? *Rom J Morphol Embryol* 2019c, 60(2): 567-572.
119. Cucu AI, Costea CF, Perciaccante A, Turliuc S, Ciocoiu M, Turliuc MD. The Anatomy of Papal Tiara: A Story about Popes' Contribution and Protection of Anatomists. Journal of Religion and Health 2019d, 58(4): 1307-1327.
120. Cucu AI, Costea CF, Carauleanu A, et al. Meningiomas related to the Chernobyl irradiation disaster in North-Eastern Romania between 1990 and 2015. *Rev Chim (Bucharest)* 2018, 69(6):1562-1565.
121. Cucu AI, Turliuc MD, Carauleanu A, et al. Chemical aspects of peritumoral cerebral edema in atypical meningiomas. *Rev Chim (Bucharest)* 2018a, 69:2804-2807.
122. Cucu AI, Costea CF, Poeata I, et al. Anatomical localization of atypical meningiomas: our experience on 81 patients. *Revista Medico-chirurgicala a Societatii de Medici si Naturalisti* din Iasi 2018b, 122:744-752.
123. Cucu AI, Costea CF, Turliuc MD, et al. Mirror, mirror on the wall, who's the fairest of them all? Atypical meningioma associated with multiple meningiomas. *Romanian Neurosurgery* 2018c, 32(4):563-572.

124. Cucu AI, Costea CF, Dumitrescu GF, et al. Ancient history of pituitary stalk. *Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology* 2018d, 17(1): 83-86.
125. Cucu AI, Costea CF, Sava A, et al. Neurovascular compression syndrome in trigeminal neuralgia, *Revista Română de Anatomie Funcțională și Clinică Macro-și Microscopică și de Antropologie* 2018e, 17(3): 199-203.
126. Cunningham A. *The anatomist anatomist's: An experimental discipline in enlightenment Europe*. New York: Routledge, 2016.
127. Cushing H. The cranial hyperostoses produced by meningeal endotheliomas. *Arch Neurol Psychiatry* 1922, 8:139-154.
128. Czarnetzki A, Schwaderer E, Pusch CM. Fossil record of meningioma. *Lancet* 2003, 362:408.
129. Dandy WE. Concerning the cause of trigeminal neuralgia. *Am J Surg* 1934, 24:447-455.
130. Darsaut TE, Lanzino G, Lopes MB, Newman S. An introductory overview of orbital tumors. *Neurosurg Focus* 2001, 15; 10(5):E1.
131. Davagnanam I, Brew S. Subarachnoid hemorrhage with cerebral vein thrombosis and aneurysmal disease: a treatment conundrum a case report. *Interventional Neuroradiology* 2008, 14:335-338.
132. David R. The art of healing in ancient Egypt: a scientific reappraisal. *Lancet* 2008, 327:1802-1803.
133. Davis M, Lucatorto M. Mannitol revisited. *Journal of Neuroscience Nursing* 1994, 26:170-174.
134. Diab M. *Lexicon Orthopaedic Etymology*. Amsterdam: Harwood Academic Publishers, 1999.
135. De Barros Filho TEP, Oliveira RP, De Barros EK, et al. Ferimento por projétil de arma de fogo na coluna vertebral: estudo epidemiológico, 2002. www.plataformainterativa2.com/coluna/html/revistacol una/volume1/ ferimento_ projetil.htm
136. De Cock P. *Erythritol*. In: O'Brien Nabors L (ed) *Alternative sweeteners*. Boca Raton: CRC Pres, 2012.
137. De Divitiis O, d'Avella E, de Notaris M, et al. The (R)evolution of Anatomy. *World Neurosurg* 2019, 127:710-735.
138. De Luzzi M. *Anathomia corporis humani*. Venice: Bernhandis Venetus de Vitalibus, 1316.
139. De Moragas J. *De Carlos I Emperador a Carlos II El Hechizado*. Barcelona: Juventud, 1970.
140. De Notaris M, Palma K, Serra L. A three-dimensional computer-based perspective of the skull base. *World Neurosurg* 2014, 82(6 Suppl):S41-48.
141. Déjérine J. *Anatomie des centres nerveux*. Paris, Rueff et Cie, Volume 1, 1895.
142. Delgado-López PD, Martin-Velasco V, Castilla-Díez JM, et al. Dexamethasone treatment in chronic subdural haematoma. *Neurocirugia* 2009; 20(4):346-359.

143. Demaree HA, Schmeichel BJ, Robinson JL, et al. Up- and down-regulating facial disgust: Affective, vagal, sympathetic, and respiratory consequences. *Biol Psychol* 2006, 71:90-99.
144. Derenzini M, Trerè D. Silver-stained Nucleolar Organizer Regions (AgNOR). *Pathologica* 2001, 93(2):99-105.
145. Derome PJ, Guiot G. Bone problems in meningiomas invading the base of the skull. *Clin Neurosurg* 1978, 25:435-451.
146. Desai P, MacEwen CJ, Baines P, Minaissian DC. Epidemiology and implications of ocular trauma admitted to hospital in Scotland. *J Epidemiol Community Health* 1996, 50:436-441.
147. Di Cristofori A, Del Bene M, Locatelli M et al. Meningioma and bone hyperostosis: expression of bone stimulating factors and review of literature. *World Neurosurg* 2018, 115:e774-e781.
148. Dobrowsky W. Treatment of choroid metastases. *Br J Radiol* 1988, 61(722):140-142.
149. Docampo J, Gonzalez N, Muñoz A, et al. Neurovascular study of the trigeminal nerve at 3 t MRI. *Neuroradiol J* 2015, 28:28-35.
150. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol* 2012, 14(5):1-49.
151. Domenicucci M, Santoro A, D'Osvaldo DH, et al. Multiple intracranial meningiomas. *J Neurosurg* 1989, 70:41-44.
152. Draf W, Carrau RL, Bockmuehl U. E*ndonasal endoscopic surgery of skull base tumors: an interdisciplinary approach*. New York: Thieme, 2015.
153. Drevelegas A, Karkavelas G, Chourmouzi D, Boulogianni G, Petridis A, Dimitriadis A. *Meningeal tumors, in Imaging of brain tumors with histological correlations,* Drevelegas A (ed), Berlin: Springer-Verlag, 2002.
154. Dumitrescu GF, Indrei A, Husseini M El, et al. Posterior fossa Meningiomas: correlation between site of origin and pathology. *Romanian Neurosurgery* 2010, 17(3): 327-338.
155. Dumitrescu GF, Indrei A, Poeata I, et al. Diagnostic value of silver nitrate staining for nucleolar organizer regions in cerebral astrocytic tumors. *Romanian Neurosurgery* 2010a, 17 (1):64-72.
156. Dumitrescu G, Indrei A, Turliuc D, et al. Corrélations démographiques et histopathologiques sur 103 méningiomes intracrâniens diagnostiques dans l'hopital clinique d'urgences "Prof. Dr. N. Oblu" Iasi. *Revista Română de Anatomie Funcțională și Clinică Macro-și Microscopică și de Antropologie* 2009, 8(4): 548-558.
157. Dunlop J. *Memoirs of Spain during the reigns of Philip IV and Charles II from 1621 to 1700*.Volume II. Edinburgh: Thomas Clark, 1834.
158. Dunglison R. *Dunglison's American Medical Library. Counter-Irritation, Its Principles and Practice*. Philadelphia: A. Waldie, 1838.
159. Dunya IM, Rubin PA, Shore JW. Penetrating orbital trauma. *Int Ophthalmol Clin* 1995, 35(1):25-36.
160. Dupuytren G. *On the Injuries and Diseases of Bones*. London: F. Le Gros Clark, 1847.

161. Durand A, Labrousse F, Jouvet A, et al. WHO grade II and III meningiomas: a study of prognostic factors. *J Neurooncol* 2009, 95(3):367-375.
162. Durant W, Durant A. The story of civilization: the age of Louis XIV, 1648–1715. New York: Simon & Schuster, 1963.
163. Dziedzic T, Szczudlik A, Klimkowicz A, et al. Is mannitol safe for patients with intracerebral hemorrhages? Renal considerations. *Clin Neurol Neurosurg* 2003, 105(2):87-89.
164. Edgerton MT, Persing JA, Jane JA. The surgical treatment of fibrous dysplasia with emphasia with emphasis on recent contributions from cranio-maxillo-facial surgery. *Ann Surg* 1985, 202:459-479.
165. Edlmann E, Giorgi-Coll S, Whitfield PC, et al. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation* 2017, 14(1):1-13.
166. Elangovan T, Mani NJ, Malathi N. Argyrophilic nucleolar organizer regions in inflammatory, premalignant, and malignant oral lesions: A quantitative and qualitative assessment. *Indian J Dent Res* 2008, 19(2):141-148.
167. Ellenbogen RG, Abdulrauf SI, Sekhar LN. *Principles of neurological surgery, Greek and Byzantine period: the origins of neurosurgery.* Philadelphia: Elsevier Saunders, 2012.
168. Ereth MH, Schaff M, Ericson EF, et al. Comparative safety and efficacy of topical hemostatic agents in a rat neurosurgical model. *Neurosurgery* 2008, 63(4) (Suppl 2):369-372.
169. Ersoy G, Kaynak MF, Yilmaz O, et al. Hemostatic effects of microporous polysaccharide hemosphere in a rat model with severe femoral artery bleeding. *Adv Ther* 24:485-492, 2007.
170. Esiri M, Oppenheimer RD. *Diagnostic Neuropathology*. Oxford: Blackwell Scientific Publications, 1989.
171. Eskandary H, Sabba M, Khajehpour F, Eskandari M. Incidental findings in brain computed tomography scans of 3000 head trauma patients. *Surg Neurol* 2005, 63:550-553.
172. Eslami M, Baghaee F, Alaeddini M. Diagnostic value of silver–stained nucleolar organizer regions in osteosarcoma, fibrous dyaplasia and ossifying fibroma of the Jaws. *Acta Medica Iranica* 2005, 43(4):243-248.
173. Evans TW, Crane EA, Swinburne J, Johnston WE. *History of the American Ambulance Established in Paris During the Siege of 1870–1871*. London: S. Low, Marston Low and Searle, 1873.
174. Fagan GG. *The Lure of the Arena: Social Psychology and the Crowd at the Roman game.* Cambridge: Cambridge University Press, 2011.
175. Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol* 2014, 15(7): e279-89.
176. Fandino W. Understanding the physiological changes induced by mannitol: From the theory to the clinical practice in neuroanaesthesia. *J Neuroanaesthesiol Crit Care* 2017, 4:138-146.

177. Fang L, You H, Chen B, et al. Mannitol is an independent risk factor of acute kidney injury after cerebral trauma: a case-control study. *Ren Fail* 2010, 32(6):673-679.
178. Farmer JC, Vaccaro AR, Balderston RA, et al. The changing nature of admissions to a spinal cord injury center: violence on the rise. *J Spinal Disord* 1998, 11(5):400-403.
179. Ferriani S. Professional jealousy. *BMJ* 2004, 328(7444):328-887.
180. Festinger L. A theory of social comparison processes. *Human Relations* 1954, 7:117-140.
181. Figley CR. *Compassion fatigue as secondary traumatic stress disorder: An overview.* In Figley CR (Ed.), *Compassion fatigue*. New York: Brunner/Mazel, 1995.
182. Filippidis A, Kapsalaki E, Patramani G, Fountas KN. Cerebral venous sinus thrombosis: review of the demographics, pathophysiology, current diagnosis, and treatment. *Neurosurg Focus* 2009, 27(5):E3.
183. Finger S. *Origins of Neuroscience. The History of Explorations into Brain Function*. New York: Oxford University Press, 1994.
184. Flynn BC. Hyperkalemic cardiac arrest with hypertonic mannitol infusion: The strong ion difference revisited. *Anesth Analg* 2007, 104:225-226.
185. Foucault M. *The History of Sexuality. The Care of the Self*. Vol. 3. New York: Random House, 1988.
186. Fox JL, AI-Mefty O. Suprasellar arachnoid cysts: an extension of the membrane of Liliequist. *Neurosurgery* 1980, 7:615-618.
187. Freeman N, Welbourne J. Osmotherapy: science and evidence-based practice. *BJA Education* 2018, 18(9): 284e290.
188. French RK. *Dissection and Vivisection in the European Renaissance.* Aldershot: Ashgate, 1999.
189. Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malfor-mations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye ab-normalities. *Arch Dermatol* 1996, 132(3):307-311.
190. Friedman AB, Osberg RH. Gawain's girdle as traditional symbol. *J Am Folklore* 1977, 90:301-315.
191. Fumarel R, Murgoi G, Albert P, et al. Increase of cisplatin therapeutical index through optical irradiation: a case study of choroidal metastasis. *Rom Rep Phys* 2008, 60(3):877-884.
192. Galarza M, Porcar OP, Gazzeri R, Martínez-Lage JF, Microporous Polysaccharide Hemospheres (MPH) for cerebral hemostasis: a preliminary report. *World Neurosurg* 2011, 75(3-4):491-494.
193. Galicich JH, French LA. Use of dexamethasone in the treatment of cerebral edema resulting from brain tumors and brain surgery. *Am J Pract Dig Treat* 1961, 12:169-174.
194. Garcia-Escudero López A, Arruza Echevarría A, Padilla Nieva J, Puig Giró R. Carlos II: del hechizo a su patología génito-urinaria. *Arch Esp Urol* 2009, 62(3):179-185.
195. Gargantilla P. *Enfermedades de los Reyes de España, Los Austrias: de la locura de Juana a la impotencia de Carlos II el Hechizado*. Madrid: La Esfera de Los Libros, 2005.

196. Gaudio E, Memoli A. (XXXX). Brief summary of the faculty's history. The Teaching of Medicine in Roma. http://www.farma ciame dicin a.uniro ma1.it/en/facul ty/about -us/brief -summa ry-facul tys-history
197. Gazzeri R, Galarza M, Neroni M, et al. Minimal craniotomy and matrix hemostatic sealant for the treatment of spontaneous supratentorial intracerebral hemorrhage. *J Neurosurg* 2009, 110:939-942.
198. Gelabert M, Fernández JM, López E, García-Allut A. Hematoma subdural crónico en el paciente mayor de 80 años. *Neurocirugía* 2001, 12:325-330.
199. Gentry LR, Smoker WR, Turski PA, et al. Suprasellar arachnoid cysts: 1. CT recognition. *Am J Neuroradiol* 1986, 7(1):79-86.
200. Georgiou K, Larentzakis A, Papavassiliou AG. Surgeons' and surgical trainees' acute stress in real operations or simulation: A systematic review. *Surgeon* 2017, 15(6):355-365.
201. Gilman SL. Lam Qua and the development of a westernized medical iconography in China. *Med Hist* 1986, 30(1):57-69.
202. Giuffrè G, Barresi V, Catalano A, et al. Actinic keratosis associated with squamous and basal cell carcinomas: an evaluation of neoplastic progression by standardized AgNOR analysis. *Europ J Histochem* 2008, 52(1):53-60.
203. Giuffrè R. Successful radical removal of an intracranial meningioma in 1835 by Professor Pecchioli of Siena. *J Neurosurg* 1984, 60:47-51.
204. Glaser JS. *Topical diagnosis: the optic chiasm*. In: Glaser JS (Ed) *Neuro-ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 1999.
205. Glynn RJ, Seddon JM, Berlin BM. The incidence of eye injuries in New England. *Arch Ophthalmol* 1988, 106:785-789.
206. Gondim Fde A, Aiyagari V, Shackleford A, Diringer MN. Osmolality not predictive of mannitol-induced acute renal insufficiency. *J Neurosurg* 2005, 103(3):444-447.
207. Goodrich JT. *Landmarks in the history of neurosurgery.* In: Rengachary SS, Ellenbogen RG (eds) *Principles of neurosurgery*. Philadelphia: Elsevier Mosby, 2012.
208. Goodrich JT. A millennium review of skull base surgery. *Childs Nerv Syst* 2000, 16:669-685.
209. Göppner D, Leverkus M. Basal cell carcinoma: from the molecular understanding of the pathogenesis to targeted therapy of progressive disease. *J Skin Cancer* 2011, 2011: 650258.
210. Gordon SA, Stage KH, Tansey KE, Lotan Y. Conservative management of priapism in acute spinal cord injury. *Urology* 2005, 65(6):1195-1197.
211. Gray H. Anatomy of the Human Body. Philadelphia: Lea and Febiger, 1918.
212. Grembecka M. *Sugar alcohols as sugars substitutes in food industry*. In: Merillon JM, Ramawat KG (eds). *Sweeteners. Reference Series in Phytochemistry*. Cam: Springer, 2018
213. Grier JT, Batchelor T. Low-grade gliomas in adults. *Oncologist* 2006, 11(6):681-693.
214. Gross JJ, Levenson RW. Hiding feelings: The acute effects of inhibiting negative and positive emotion. *J Abnorm Psychol* 1997, 106, 95-103.

215. Grostern RJ. *Basal cell carcinoma*. In: Older JJ (ed). *Eyelid tumors: clinical diagnosis and surgical treatment*. 2nd edition, Manson Publishing, Ltd., 2003.
216. Guidetti B, Giuffrè R, Valente V. Italian contribution to the origin of neurosurgery. *Surg Neurol* 1983, 20:335-346.
217. Gurkanlar D, Er U, Sanli M, et al. Peritumoral brain edema in intracranial meningiomas. *J Clin Neurosci* 2005, 12, 750-753.
218. Gurman GM, Klein M, Weksler N. Professional stress in anesthesiology: a review. *J Clin Monit Comput* 2012, 26:329-335.
219. Gutiérrez Rodilla BM. La Clavis sanationis, de Simón de Cordo (siglo XIII). *Panace@* 2004, 5:287-288.
220. Haberland C, Martin H, Guski H, et al. AgNOR analysis of astrocytoma in childhood. *Zentrallbl Neurochir* 1996, 57(1):5-11.
221. Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangio-mas: New clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics* 2006, 117:698-703.
222. Hale AT, Wang L, Strother MK, Chambless LB. Differentiating meningioma grade by imaging features on magnetic resonance imaging. *J Clin Neurosci* 2018, 48:71-75.
223. Hall M. *On the Diseases and Derangements of the Nervous System: In Their Primary Forms and in Their Modifications by Age, Sex, Constitution, Hereditary Predisposition, Excesses, General Disorder, and Organic Disease*. London, England: H. Baillière, 1841.
224. Hammouche S, Clark S, Wong AH, et al. Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. *Acta Neurochir (Wien*) 2014, 156(8):1475-1481.
225. Han J, Zhang Q, Kong F, Gao Y. The incidence of invasion and metastasis of nasopharyngeal carcinoma at different anatomic sites in the skull base. *Anat Rec (Hoboken)* 2012, 295:1252-1259.
226. Handa J, Okamoto K, Sato M. Arachnoid cyst of the middle cranial fossa: report of bilateral cysts in siblings. *Surg Neurol* 1981, 16:127-130.
227. Hara A, Sakai N, Yamada H, et al. Nucleolar organizer regions in vascular and neoplastic cells of human gliomas. *Neurosurg* 1991, 29(2):211-215.
228. Harsha KJ, Kesavadas C, Chinchure S, et al. Imaging of vascular causes of trigeminal neuralgia. *J Neuroradiol* 2012; 39:281-289.
229. Hart ES, Kelly MH, Brillante B, et al. Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. *J Bone Miner Res* 2007, 22(9):1468-1474.
230. Hashemi F, Babaheidarian P, Dabiran S. Are osteopontin and Ki67 expressions different in various histologic grades of meningioma? An Iranian experience. *Iran J Pathol* 2015, 10(4):253-257.
231. Hastings J. *A Dictionary of the Bible.* Honoloulu: The Minerva Group, 2004.
232. Hatch M, Ron E, Bouville A, et al. The Chernobyl disaster: cancer following the accident at the Chernobyl nuclear power plant. *Epidemiol Rev* 2005, 27, p.56-66.

233. Hayashi K, Iwasaki Y, Yanagi K. Herpes simplex virus type 1-induced hydrocephalus in mice. J Virol 1986, 57(3):942-951.
234. Haymaker W, Rubinstein LJ, Miquel J. Brain tumors in irradiated monkeys. *Acta Neuropathol* 1972, 20:267-277.
235. Heick A, Mosdal C, Jorgensen K, Klinken L. Localized cranial hyperostosis of meningiomas: a result of neoplastic enzymatic activity? *Acta Neurol Scand* 1993, 87:243-247.
236. Hemphill JC III, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001, 32:891-897.
237. Henke G, Kucinski T, Simon M, Herrlinger U. Nebenwirkungen der therapie von Hirntumoren. *Onkologe* 2006, 12(6):546-555.
238. Herodotus. *Herodotus, Books I-II, with an English translation by A.D. Godley*. Cambridge: Harvard University Press, 1920.
239. Herrlinger R, Feiner E. Why did Vesalius not discover the fallopian tubes? *Med Hist* 1964, 8:335-341.
240. Herweh C, Kress B, Rasche D, et al. Loss of anisotropy in trigeminal neuralgia revealed by diffusion tensor imaging. *Neurology* 2007; 68: 776-778.
241. Heyer GL, Dowling MM, Licht DJ *et al.* The cerebral vasculopathy of PHACES syndrome. *Stroke* 2008, 39(2): 308-316.
242. Hippocrates. *On nature of bones.* In: Litre PE (Ed) *Oeuvres Completes d'Hippocrate*. Vol. 9. Amsterdam: AM Hakkert, 1982.
243. Honeybul S, O'Hanlon S, Ho KM. Decompressive craniectomy for severe head injury: does an outcome prediction model influence clinical decision-making? *J Neurotrauma* 2011, 28:13-19.
244. Horton JC. Wilbrand's knee of the primate optic chiasm is an artefact of monocular enucleation. *Trans Am Ophthalmol Soc* 1997, 95:579-609.
245. Howard IP. *Perceiving in depth. Basic mechanisms*, vol 1. New York: Oxford University Press, 2012.
246. Howard IP, Rogers BJ. *Binocular vision and stereopsis*. New York: Oxford University Press, 1995.
247. Hoyt WF, Luis O. Visual fiber anatomy in the infrageniculate pathway of the primate. *Arch Ophthalmol* 1962, 68:124-136.
248. Hsu DW, Efird JT, Hedley-Whyte ET. MIB-1 (Ki-67) index and transforming growth factor-alpha (TGF alpha) immunoreactivity are significant prognostic predictors for meningiomas. *Neuropathol Appl Neurobiol* 1998, 24(6):441–452.
249. Huang H, Buhl R, Hugo HH, et al. Clinical and histological features of multiple meningiomas compared with solitary meningiomas. *Neurol Res* 2005, 27:324-332.
250. Humphreys MR, Castle EP, Andrews PE, et al. Microporous polysaccharide hemospheres for management of laparoscopic trocar injury to the spleen. *Am J Surg* 2008a, 195(1):99-103.
251. Humphreys MR, Lingeman JE, Terry C, et al. Renal injury and the application of polysaccharide hemospheres: a laparoscopic experimental model. *J Endourol* 2008b, 22(6):1375-1381.

252. Hussein K. Quelques specimens de pathologie osseuse chez les anciens Egyptiens. *Bull de l'Inst d'Egypte* 1951, 32:11-17.
253. Hussein K. *A description of some bones examined.* In: Saad Z (ed). Royal Excavations at Saqqara and Helwan, 1941-1945. Suppl. aux Annales du Service des Antiquites d'Egypte, 1947.
254. Hyrtl J. *Onomatologia Anatomica.* Wien: Wilhelm Braum€uller, 1880.
255. Ildan F, Tuna M, Gocer AI, et al. Correlation of the relationships of brain-tumor interfaces, magnetic resonance imaging, and angiographic findings to predict cleavage of meningiomas. *J Neurosurg* 1999, 91:384-390.
256. Inamura T, Nishio S, Takeshita I, et al. Peritumoral brain edema in meningiomas-influence of vascular supply on its development. *Neurosurgery* 1992, 31:179-185.
257. Iordache A, Munteanu R, Coșman M, Turliuc DM. Intracranial pressure monitoring in neurosurgery department in Iași - latest developments. *Romanian Neurosurgery* 2012, 19(1).
258. Jamjoom ZA, Okamoto E, Jamjoom AH, et al. Bilateral arachnoid cysts of the sylvian region in female siblings with glutaric aciduria type I. Report of two cases. *J Neurosurg* 1995, 82(6):1078-1081.
259. Janczukowicz J. The prognostic role of proliferation activity in human CNS tumors: the determination of AgNOR, PCNA and Ki-67 expression. Part 1: AgNOR expression in CNS tumors. *Folia Neuropathol* 2003, 41(2):97-101.
260. Janin H. *The university in medieval life, 1179–1499*. Jefferson/North Carolina/London: McFarland and Company, 2008.
261. Jardin A, Paré A. *The highpoint of French medicine and surgery during the Renaissance*. In: Schultheiss D, Musitelli S, Stief CG, Jonas U (eds). *Classical Writings on Erectile Dysfunction. An Annotated Collection of Original Texts from Three Millennia*. Berlin: ABW Wissenschaftsverlag, 2005.
262. Jham R, Shukla S, Acharya S, et al. Correlation of the proliferative markers (AgNOR and Ki-67) with the histological grading of the glial tumors. *J Datta Meghe Inst Med Sci Univ* 2017, 12:211-7.
263. Johnson S. *Dictionnary of the English Language with Numerous Corrections and with the Addition of Several Thousand Works and Also with Addition to the History of the Language and to the Grammar by H.J. Todd*. Vol. 2. 2nd Ed. London: Longman, Rees, Orme, Brown & Green, 1827.
264. Kachhela J, Tang CM, Shin RK. Wilbrand's knee revisited. *The 42nd annual meeting of North American neuro-ophthalmology society*, 2016.
265. Kalfas IH, Little JR. Postoperative hemorrhage: a survey of 4,992 intracranial procedures. *Neurosurgery* 1988, 23:343-347.
266. Kamen H. *Spain, 1469–1714: A society of conflict*. London: Longman, 1983.
267. Kaneda K, Baker MT, Han TH, Weeks JB, Todd MM. Pharmacokinetic characteristics of bolus-administered mannitol in patients undergoing elective craniotomy. *J Clin Pharmacol* 2010, 50(5):536-543.
268. Kang DJ. Women's healing spaces: a case study of the female patients and their foreign doctor in the Canton Hospital, 1835–55. *J Comp As Dev* 2012, 11:3-34.

269. Karabağli P, Sav A. Proliferative indices (MIB-1) in meningiomas: correlation with the histological subtypes and grades. *J Neurol Sci* 2006, 23(4):279–286.
270. Karakas C. Paget's disease of the breast. *J Carcinog* 2011, 10:31-31.
271. Karamanou M, Androutsos G. Completing the puzzle of blood circulation: The discovery of capillaries. *Italian Journal of Anatomy and Embryology 2010, 115:*175-179.
272. Katz BJ, Nerad JA. Ophthalmic manifestations of fibrous dysplasia: a disease of children and adults. *Ophthalmology* 1998, 105:2207-2215.
273. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. *JAMA* 1999, 282:36-39.
274. Kawaguchi M, Kato H, Tomita H, et al. Imaging Characteristics of Malignant Sinonasal Tumors. *J Clin Med* 2017, 6(116):1-25.
275. Kaye A, Grogono A. *Fluid and electrolyte physiology*. In: Miller RD (ed). *Anesthesia*. 5th ed. Philadelphia: Churchill Livingstone, 2000.
276. Kemper WH. The world's anatomists: concise biographies of anatomic masters, from 300 B.C. to the present time, whose names have adorned the literature of the medical profession. Philadelphia: Blakiston's Son & Company, 1905.
277. Kepes JJ. Presidential address: the histopathology of meningiomas. A reflection of origins and ex-pected behavior? *J Neuropathol Exp Neurol* 1986, 45(2):95-107.
278. Kim MY, Park JH, Kang NR, et al. Increased risk of acute kidney injury associated with higher infusion rate of mannitol in patients with intracranial hemorrhage. *J Neurosurg* 2014, 120(6):1340-1348.
279. Kim SW, Youn SK, Kim J T, et al. Management of an unusual craniofacial impalement injury by a metallic foreign body. *J Craniofac Surg* 2012, 23(2):140-146.
280. Kim BW, Kim MS, Kim SW, et al. Peritumoral brain edema in meningiomas: correlation of radiologic and pathologic features. *J Korean Neurosurg Soc* 2011, 49 (1):26-30.
281. Kin T, Nakatomi H, Shojima M, et al. A new strategic neurosurgical planning tool for brainstem cavernous malformations using interactive computer graphics with multimodal fusion images. *J Neurosurg* 2012, 117:78-88.
282. King AD, Lam WW, Leung SF, et al. MRI of local disease in nasopharyngeal carcinoma: tumour extent vs tumour stage, *Brit J Radiol* 1999; 72:734-741.
283. Klančnik M, Ivanišević P, Lupi-Ferandin S, et al. Penetrating orbitocranial injury. Acta Clin Croat 2018, 57(4):792-796.
284. Kleihues P, Cavenee WK. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Nervous System*. Lyon: IARC Press, 2000.
285. Koh YC, Yoo H, Whang GC, et al. Multiple meningiomas of different pathological features: case report. *J Clin Neurosci* 2001, 1(8 Suppl.):40-43.
286. Kolias AG, Edlmann E, Thelin EP, et al. Dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial: study protocol for a randomised controlled trial. *Trials* 2018, 19(1):1-14.
287. Kolles H, Niedermayer I, Schmitt C, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007, 114:97-109.

288. Kompanje EJ. A patient with a large intra- and extracranial tumor, most probably a primary extradural meningioma, described in 1730. *J Neurooncol* 2004, 67:123-125.
289. König P, Waanders R, Witzmann A, et al. Cerebrolysin in traumatic brain injury – a pilot study of a neurotrophic and neurogenic agent in the treatment of acute traumatic brain injury. *J Neurol Neurochir Psychiatr* 2006, 7:12-20.
290. Koskinen S, Alaranta H. Traumatic brain injury in Finland 1991–2005: a nationwide register study of hospitalized and fatal TBI. *Brain Inj* 2008, 22:205-214.
291. Kowianski P, Dziewiatkowski J, Kowianska J, Morys J. Comparative anatomy of the claustrum in selected species: A morphometric analysis. *Brain Behav Evolut* 1999, 53:44-54.
292. Koyuncu E, Taşoğlu Ö, Orhan A, et al. Recurrent priapism in spinal cord injury: A case report. *J Spinal Cord Med* 2019, 10:1-3.
293. Kreusel KM, Wiegel T, Stange M, et al. Choroidal metastasis in disseminated lung cancer: frequency and risk factors. *Am J Ophthalmol* 2002, 134(3):445-447.
294. Kuerer HM, Eberlein TJ, Pollock RE, et al. Career satisfaction, practice patterns and burnout among surgical oncologists: report on the quality of life of members of the Society of Surgical Oncology. *Ann Surg Oncol* 2007, 14:3043-3053.
295. Kumar A, Pandey PN, Ghani A, Jaiswal G. Penetrating spinal injuries and their management. *J Craniovertebr Junction Spine* 2011, 2(2):57-61.
296. Kuncz A, Vφrφs E, Barzó P, et al. Comparison of clinical symptoms and magnetic resonance angiographic (MRA) results in patients with trigeminal neuralgia and persistent idiopathic facial pain. Medium term outcome after microvascular decompression of cases with positive MRA findings. *Cephalalgia* 2006, 26:266-276.
297. Kupcha P, An HS, Cotler JM. Gunshot wounds to the cervical spine. *Spine* 1990, 15(10):1058-1063.
298. Kuznetsov SA, Cherman N, Riminucci M, et al. Age-dependent demise of GNAS-mutated skeletal stem cells and "normalization" of fibrous dysplasia of bone. *J Bone Miner Res* 2008, 23:1731-1740.
299. Labadie EL, Glover D. Physiopathogenesis of subdural hematomas: part II: inhibition of growth of experimental hematomas with dexamethasone. *J Neurosurg* 1976, 45:393-397.
300. Landow H, Kabat EA, Newman W. Distribution of alkaline phosphatase in normal and neoplastic tissues of the nervous system. *Arch Neurol Psychiatry* 1942, 48:518-530.
301. Laws ER Jr. Neurosurgery's man of the century: Harvey Cushing - the man and his legacy. *Neurosurgery* 1999, 45:977-982.
302. Le Bihan D. Molecular diffusion, tissue microdynamics and microstructure. *NMR Biomed* 1995, 8:375-386.
303. Lebby PC. *Brain Imaging: A Guide for Clinicians.* New York: Oxford University Press, 2013.
304. Lebensohn JE. Wollaston and hemianopsia. *Am J Ophthalmol* 1941, 24:1053-1056.
305. Leber KA, Berglfff J, Pendl G. Dose-response of visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *J Neurosurg* 1998, 88(1):43-50.

306. Lee JH, Sade B, Choi E, et al. Meningothelioma as the predominant histological subtype of midline skull base and spinal meningioma. *J Neurosurg* 2006a, 105(1):60-64.
307. Lee JH, Tobias S, Kwon JT. Wilbrand's knee: does it exist? *Surg Neurol* 2006b, 66:11-17.
308. Lee JS, Fitzgibbon E, Butman JA, et al. Normal vision despite narrowing of the optic canal in fibrous dysplasia. *N Engl J Med* 2002, 347:1670-1676.
309. Lee J, Lee J, Oum B, et al. Orbitocranial injury caused by wood. *Korean J Ophthalmol* 1999, 13:128-132.
310. Lee SB, Saw SM, Au Eong KG, et al. Incidence of eyelid cancers in Singapore from 1968 to 1995. *Br J Ophthalmol* 1999a, 83(5):595-597.
311. Lemire R, Loeser J, Leech R, Alvord EJ. *Normal and abnormal development of the human nervous system*. New York: Harper & Row, 1975.
312. Li P, Yang Z, Wang Z, et al. Clinical features of clear cell meningioma: a retrospective study of 36 cases among 10,529 patients in a single institution. *Acta Neurochir (Wien)* 2016, 158(1):67-76.
313. Li YZ, Cai PQ, Xie CM, et al. Nasopharyngeal cancer: impact of skull base invasion on patients prognosis and its potential implications on TNM staging. *Eur J Radiol* 2013, 82:107-111.
314. Lifshutz J, Colohan A. A brief history of therapy for traumatic spinal cord injury. *Neurosurg Focus* 2004; 16:E5.
315. Lin SY, Tang SC, Tsai LK, *et al.* Incidence and risk factors for acute kidney injury following mannitol infusion in patients with acute stroke: A retrospective cohort study. *Medicine (Baltimore)* 2015, 94:e2032.
316. Lindberg DC. Theories of vision from Al-Kindi to Kepler. Chicago: University of Chicago Press, 1976.
317. Lingsma HF, Roozenbeek B, Steyerberg EW, et al. Early prognosis in traumatic brain injury: from prophecies to predictions. *Lancet Neurol* 2010, 9:543-554.
318. Linn J, Peters F, Moriggl B, et al. The jugular foramen: imaging strategy and detailed anatomy at 3T. *AJNR Am J Neuroradiol* 2009, 30: 34-41.
319. Littell E. Littell's living age. Boston: E Littell & Company, 1849.
320. Liu L, Liang S, Li L, et al. Prognostic impact of magnetic resonance imaging detected cranial nerve involvement in nasopharyngeal carcinoma. *Cancer* 2009, 115:1995-2003.
321. Loew F, Pertuiset B, Chaumier EE, Jaksche H. Traumatic, spontaneous and postoperative CSF rhinorrhea. *Adv Tech Stand Neurosurg* 1984, 11:169-207.
322. Lonser RR, Walbridge S, Vortmeyer AO, et al, Induction of glioblastoma multiforme in nonhuman primates after therapeutic doses of fractionated whole-brain radiation therapy. *J Neurosurg* 2002, 97(6):1378-1389.
323. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organisation Classification of Tumours of the central nervous system: a summary. *Acta Neuropathol* 2016a, 131:803-820.

324. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *World Health Organization Histological Classification of Tumours of the Central Nervous System*. 4th ed. Lyon: International Agency for Research on Cancer, 2016b.
325. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumors of the central nervous system. *Acta Neuropathol* 2007, 114:97-109.
326. Louis DN, Scheitauer BW, Budka H, von Deimling A, Kepes JJ. *Meningiomas.* In: Kleihues P, Cavenee WK (eds). *Pathology and Genetics of Tumors of the Nervous System*. Lyon: IARC Press, 2000.
327. Louis A. *Mémoire sur les tumeurs fongueuses de la dure-mère*. Mem Acad Roy Chir Paris 1774, 5:1-59.
328. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. *Brain* 2001; 124: 2347-2360.
329. Love S, Hilton DA, Coakham HB. Central demyelination of the Vth nerve root in trigeminal neuralgia associated with vascular compression. *Brain Pathol* 1998; 8:1-11.
330. Lue TF. *Physiology of penile erection and pathophysiology of erectile dysfunction and priapism*. In Walsh PC, Retik AB, Vaughan ED Jr, et al (Eds). *Campbell's Urology*, 8th ed. Philadelphia: WB Saunders, 2002.
331. Lutz J, Linn J, Mehrkens JH, et al. Trigeminal neuralgia due to neurovascular compression: high spatial- resolution diffusion-tensor imaging reveals microstructural neural changes. *Radiology* 2011, 258:524-530.
332. Luys JB. *Recherches sur le système cérébro-spinal, sa structure, ses fonctions et ses maladies*. Paris: J. B. Baillière et fils, 1865.
333. Ma Z. "Nerve combing" for trigeminal neuralgia without vascular compression: report of 10 cases. *Clin J Pain* 2009, 25:44-47.
334. Maartens NF. The history of the treatment of pituitary adenomas. *Endocrine* 2005, 28:9-26.
335. Macchi V, Porzionato A, Morra A, De Caro R. Gabriel Falloppius (1523-1562) and the facial canal. *Clin Anat* 2014, 27:4-9.
336. MacEwen CJ. Ocular injuries. *JR Coll Surg Edinb* 1999, 44:317-323.
337. Mackerle Z, Gal P. Unusual penetrating head injury in children: personal experience and review of the literature. *Child's Nerv Syst* 2009, 25:909-913.
338. Mahmood A, Caccamo DV, Tomecek FJ, et al. Atypical and malignant meningiomas: a clini-copathological review. *Neurosurgery* 1993, 33:955-963.
339. Majdan M, Plancikova D, Brazinova A, et al., Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health* 2016, 1(2):e76-e83.
340. Majdan M, Mauritz W. Unintentional fall-related mortality in the elderly: comparing patterns in two countries with different demographic structure. *BMJ Open* 2015, 5: e008672.
341. Malacarne, V. *Nuova Esposizione della vera struttura del cervelletto umano.* Torino: Arduino, 1776.
342. Mangubat EZ, Byrne RW. Major intratumoral hemorrhage of a petroclival atypical meningioma: case report and review of literature. *Skull Base* 2010, 20:469-473.

343. Marentette LJ, Valentino J. Traumatic anterior fossa cerebrospinal fluid fistulae and craniofacial considerations. *Otolaryngol Clin North Am* 1991, 24:151-163.
344. Martensen RL. The Brain Takes Shape: An Early History. New York: Oxford University Press, 2004.
345. Mastronardi L, Ferrante L. Neurosurgery in Italy: the past, the present, the future. *Neurosurg Rev* 2009, 32:381-386.
346. Mastronardi L, Lunardi P, Osman Farah J, Puzzilli F. Metastatic involvement of the Meckel's cave and trigeminal nerve. A case report. *J Neurooncol* 1997, 32(1):87-90.
347. Matschke J, Addo J, Bernreuther C, Zustin J. Osseous changes in meningioma en plaque. *Anticancer Res* 2011, 31:591-596.
348. Matsushima T, Kobayashi S, Inoue T, et al. Albert L. Rhoton Jr., MD: His Philosophy and Education of Neurosurgeons. *Neurol Med Chir (Tokyo)* 2018, 58(7):279-289.
349. Mattei TA, Mattei JA, Ramina R, et al. Edema and malignancy in meningiomas. *Clinics* 2005, 60(3):201-206.
350. McAbee JH, Ragel BT, McCartney S, et al. Factors associated with career satisfaction and burnout among US neurosurgeons: results of a nationwide survey. *J Neurosurg* 2015, 123:161-173.
351. McBrien RP. *Lives of the Popes: The pontiffs from St. Peter to John Paul II*. New York: Harper Collins, 1997.
352. McCann IL, Pearlman LA. Vicarious traumatization: A framework for understanding the psychological effects of working with victims. *J Trauma Stress* 1990, 3:131-149.
353. McGovern SL, Aldape KD, Munsell MF, et al. A comparison of World Health Organization tumor grades at recurrence in patients with non-skull base and skull base meningiomas. *J Neurosurg* 2010, 112(5):925-933.
354. McKeever PE, Blaivas M. *The Brain, Spinal Cord and Meninges*. In Sternberg SS (Ed). *Diagnostic Surgical Parhology,* vol I, New-York: Raven Press Ltd., 1989.
355. McLachlan JC, Patten D. Anatomy teaching: ghosts of the past, present and future. *Med Educ* 2006, 40:243-253.
356. Meckel JF. *Manual of Descriptive and Pathological Anatomy*, second volume. London: J.-B. Baillière, Translated from German into French, with additions and notes by Jourdan, AJL, translated from the French, with notes, by Doane, AS, Henderson E, Bailey O, 1838.
357. Medvei VC. *A history of endocrinology*. Hingham: MTP Press Limited, 1982.
358. Meli MD. *Marcello Malpighi: Anatomist and physician*. Firenze: Olschki, 1997.
359. Merskey H, Bogduk N. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. Seattle: IASP Press, 1994.
360. Metry DW, Siegel DH, Cordisco MR *et al*. Comparison of disease severity among affected male versus female patients with PHACE syndrome. *J Am Acad Dermatol* 2008, 58(1):81-87.
361. Mewis L, Young SE. Breast carcinoma metastatic to the choroid. Analysis of 67 patients. *Ophthalmology* 1982, 89(2):147-151.
362. Meyer AC. *Historical Aspects of Cerebral Anatomy*. London: Oxford University Press, 1971.

363. Meyer AC. Karl Friedrich Burdach and his place in the history of neuroanatomy. *J Neurol Neurosurg Psychiatry* 1970, 33: 553-561.
364. Miah IP, Holl DC, Peul WC, et al. Dexamethasone therapy *versus* surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. *Trials* 2018, 19(1):1-10.
365. Min JH, Kang SH, Lee JB, et al. Hyperostotic meningioma with minimal tumor invasion into the skull. *Neurol Med Chir Tokyo* 2005, 45:480-483.
366. Mine S, Saeki N, Horiguchi K, et al. Craniofacial Resection for Sinonasal Malignant Tumors: Statistical Analysis of Surgical Outcome over 17 Years at a Single Institution. *Skull Base* 2011, 21(4):243-248.
367. Miscusi M, Arangi P, De Martino L. An unusual case of orbito- frontal rod fence stab injury with good outcome. *Surgery* 2013, 13:31-36.
368. Misra M, Khan GM, Mohanty AB, Rath S. An unusual orbitocranial foreign body. *Indian J Ophthalmol* 1992, 40:94-95.
369. Mocker K, Holland H, Ahnert P, et al. Multiple meningioma with different grades of malignancy: case report with genetic analysis applying single-nucleotide polymorphism array and classical cytogenetics. *Pathol Res Pract* 2011, 207:67-72.
370. Modha A, Gutin PH. Diagnosis and treatment of atypical and anaplastic meningiomas: a review. *Neurosurgery* 2005, 57(3):538-550.
371. Moon K, Filis AK, Cohen AR. The birth and evolution of neuroscience through cadaveric dissection. *Neurosurgery* 2010, 67:799-810.
372. Morris Z, Whiteley WN, Longstreth WT Jr, et al. Incidental findings on brain magnetic resonance imaging: systematic review and metaanalysis. *BMJ* 2009, 339:b3016.
373. Mortazavi MM, Adeeb N, Griessenauer CJ, et al. The ventricular system of the brain: a comprehensive review of its history, anatomy, histology, embryology, and surgical considerations. *Childs Nerv Syst* 2014, 30:19-35.
374. Moseley ME, Cohen Y, Kucharczyk J, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* 1990, 176:439-445.
375. Munteanu M, Giuri S, Roşca C, et al. Multifocal choroidal metastases from thyroid carcinoma: a case report. *Chirurgia (Bucur)* 2013, 108(2):268-272.
376. Munteanu G, Chercotă V, Giuri S. Choroidal metastasis after a bronchial carcinoid tumor. *Oftalmologia* 1994, 38(4):308-313.
377. Murat FJ, Le CQ, Ereth MH, et al. Evaluation of microporous polysaccharide hemospheres for parenchymal hemostasis during laparoscopic partial nephrectomy in the porcine model. *JSLS* 2006, 10(3): 302-306.
378. Murat FJ, Ereth MH, Dong Y, Piedra MP, Gettman MT. Evaluation of microporous polysaccharide hemospheres as a novel hemostatic agent in open partial nephrectomy: favorable experimental results in the porcine model. *J Urol* 2004, 172(3):1119-1122.
379. Muresanu DF, Ciurea AV, Gorgan RM, et al. A retrospective, Multi-Center Cohort Study Evaluating the Severity-Related Effects of Cerebrolysin Treatment on Clinical Outcomes in Traumatic Brain Injury. *CNS&Neurological Disorders - Drug Targets* 2015, 14-(5):587-599.

380. Murray J, Ehlers A, Mayou RA. Dissociation and post-traumatic stress disorder: Two prospective studies of road traffic accident survivors. *Br J Psychiatry* 2002, 180, 363-368.
381. Muscatello MR, Bruno A, Carroccio C, et al. Association between burnout and anger in oncology versus ophthalmology health care professionals. *Psychol Rep* 2006, 99(2):641-650.
382. Mzimbiri JM, Li J, Bajawi MA, et al. Orbitocranial Low-velocity penetrating injury: a personal experience, case series, review of the literature, and proposed management plan. *World Neurosurg* 2016, 87:26-34.
383. Nadeem S, Ayub M, Fawad H. Visual Outcome of Ocular Trauma. Pak J Ophthalmol 2013, 29:34-39.
384. Nair K, George T, El Beltagi A. Perineural tumour spread from colon cancer, an unusual cause of trigeminal neuropathy-a case report. *J Radiol Case Rep* 2015, 9(8):8-15.
385. Nakasu S, Nakajima M, Matsumura K, et al. Meningioma: proliferating potential and clinicoradiological features. *Neurosurgery* 1995, 37(6):1049-1055.
386. Nanda A, Bir SC, Konar S, et al. Outcome of resection of WHO Grade II menin-gioma and correlation of pathological and radiological predictive factors for recurrence. *J Clin Neuro-sci* 2016, 31:112-121.
387. Naphade PS, Keraliya AR. Facial pain in carcinoma colon. *Neurol India* 2013, 61(5):540-541.
388. Napier HE. *Florentine history, from the earliest authentic records to the accession of Ferdinand the third, grand duke of Tuscany* (Vol. 1). London: Eduard Moxon, 1846.
389. Navalón Ramón E, Ferrando Lucas MT. La enfermedad de Carlos II. *Revista Valenciana de Medicina de Familia* 2006, 22:16-19.
390. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012, 14, 48-54.
391. Nemzek WR. The trigeminal nerve. *Top Magn Reson Imaging* 1996, 8:132-154.
392. Nesterenko AV, Nesterenko VB, Yablokov AV. *Introduction: the difficult truth about Chernobyl*, In: Yablokov AV, Nesterenko VB, Nesterenko AV. *Chernobyl consequences of the catastrophe for people and the environment*. New York: New York Academy of Sciences, 2009.
393. Neuss M, Westphal M, Hansel M, et al. Clinical and laboratory findings in patients with multiple meningiomas. *Br J Neurosurg* 1988, 2:249-256.
394. Nissenson AR, Weston RE, Kleeman CR. Mannitol. *West J Med* 1979, 131:277-284.
395. Nomani AZ, Nabi Z, Rashid H, et al. Osmotic nephrosis with mannitol: Review article. *Ren Fail* 2014, 36:1169-1176.
396. Nuland SB. *Doctors: A biography of medicine*. New York: Knopf, 1989.
397. Nunez-Nateras R, Hurd KJ, Ferrigni EN, et al. Athermal nerve sparing robot-assisted radical prostatectomy: initial experience with microporous polysaccharide hemospheres as a topical hemostatic agent. *World J Urol* 2013, 31:523-527.
398. Okonkwo DO, Laws ER Jr. *Meningiomas: historical perspective.* In: Lee JH (Ed). *Meningiomas.* London: Springer, 2009.

399. O'Malley CD. *Costanzo Varolio.* In: Gillispie CC (Ed). *Dictionary of scientific biography*. New York: Charles Scribner's Sons, 1980.
400. O'Neill OR, Gilliland G, Delashaw JB, et al. Transorbital penetrating head injury with a hunting arrow: case report. *Surg Neurol* 1994, 42:494-497.
401. Onose G, Mureşanu DF, Ciurea AV, et al. Neuroprotective and consequent neurorehabilitative clinical outcomes, in patients treated with the pleiotropic drug cerebrolysin. *J Med Life* 2009, 2:350-360.
402. Orlov YuA, Shaversky AV, Mykhalyuk VS. Neuro-Oncological Morbidity In Ukrainian Preteen Children. International Conference. Health Consequences of The Chernobyl Catastrophe: Strategy Of Recovery. May 29-June 3, 2006, Kiev, Ukraine (Abstracts, Kiev).p. 16-17.
403. Orlov YuA, Sharevsky AV. Influence of ionizing radiation causing oncogenic injury to brains of children under 3 years of age. *Ukr Neurosurg J* 2003, 3.
404. Orlov YuA, Verkhoglyadova TL, Plavsky NV, Malysheva TA, Shaversky AV, Guslitzer LN. CNS tumors in children: Ukrainian morbidity for 25 years. Third International Conference. Medical consequences of the Chernobyl catastrophe: results of 15 years of investigations. June 4–8, 2001, Kiev, Ukraine (Abstracts, Kiev). p. 258-259.
405. Orlov YuA. Neurosurgical Pathology in Children in the Post-Chernobyl Period. International Scientific Conference. Actual and Prognostic Impairment of Psychological Health after the Nuclear Catastrophe in Chernobyl. May 24–28, 1995, Kiev, Ukraine (Chernobyl Doctors'association, Kiev). p. 298-299.
406. Orlov YuA. Dynamics of Congenital Malformations and Primitive Neuroectodermal Tumors. Cis Scientific Conference with International Participation. Social, Psychological and Psycho- Neurological Consequences of the Chernobyl Catastrophe, 1993, (Materials, Kiev).p. 259-260.
407. Osaki TH, Jakobiec FA, Mendoza PR, et al. Immunohistochemical investigations of orbital infantile hemangiomas and adult encapsulated cavernous venous lesions (malformation versus hemangioma). *Ophthal Plast Reconstr Surg* 2013, 29 (3):183-195.
408. Oshita J, Sogabe T, Maeda H, et al. A case of multiple meningiomas: two lesions have different clinicopathological features, respectively. *No Shinkei Geka* 2007, 35: 929-934.
409. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a "state of the science" review. *Neuro Oncol* 2014, 16(7):896-913.
410. Oury F, Yadav VK, Wang Y, et al. CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev* 2010, 24:2330-2342
411. Pacifici V. *Un carme biografico di Sisto IV del 1477*. Tivoli: Società Tiburtina di Storia e d'Arte, 1921.
412. Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* 1994, 35:1061-1064.

413. Palmer S. A Pentaglot *Dictionary of the Terms Employed in Anatomy, Physiology, Pathology, Practical Medicine, Surgery, Obstetrics, Medical Jurisprudence, Materia Medica, Pharmacy, Medical Zoology, Botany, and Chemistry, in Two Parts: Part I.* London: Longman and Co., 1845.
414. Paluzzi A, Fernandez-Miranda J, Torrenti M, Gardner P. Retracing the etymology of terms in neuroanatomy. *Clin Anat* 2012, 25:1005-1014.
415. Papacocea T, Popa E, Turliuc D, Papacocea R. The usefulness of dexamethasone in the treatment of chronic subdural hematomas. *Farmacia* 2019, 67 (1):140-145.
416. Papangelou A, Lewin JJ 3rd, Mirski MA; Stevens RD. Pharmacologic management of brain edema. Curr Treat Options Neurol 2009, 11(1):64-73.
417. Papay FA, Morales L Jr, Flaharty P, et al. Optic nerve decompression in cranial base fibrous dysplasia. *J Craniofac Surg* 1995, 6:5-10.
418. Para H. Plague, papacy and power: The effect of the black plague on the Avignon papacy. *Saber and Scroll* 2016, 5, 7-16.
419. Paravicini-Bagliani A. *The Pope's body*. Chicago/London: The Unversity of Chicago Press, 2000.
420. Parent A. The history of the basal ganglia: The contribution of Karl Friedrich Burdach. *Neuroscience and Medicine* 2012, 3:374-379.
421. Parmar IPS, Sunandan S, Nagpal RC. Pattern of ocular injuries in Haryana. *Ind J Ophthalmol* 1985, 33:141-144.
422. Pascual-Castroviejo I. Vascular and nonvascular intracranial malformation associated with external capillary hemangiomas. *Neuroradiology* 1978, 16: 82-84.
423. Pasquier D, Bijmolt S, Veninga T, et al. Atypical and malignant meningioma: outcome and prognostic factors in 119 irradiated patients a multicenter, retrospective study of the rare cancer network. *Int J Radiat Oncol Biol Phys* 2008, 71:1388-1393.
424. Paterniti S. Meningiomas surgery in Italy in the nineteenth century: historical review. *Austin Neurosurg Open Access* 2015, 2:1030.
425. Pavelin S, Becic K, Forempoher G, et al. Expression of Ki-67 and p53 in meningiomas. *Neoplasma* 2013, 60(5):480-485.
426. Pearlman LA. *Psychometric review of TSI Belief Scale, Revision* L. In: Stamm BH (Ed). *Measurement of stress, trauma and adaptation*. Lutherville: Sidron Press, 1996.
427. Pearson BE, Markert JM, Fisher WS, et al. Hitting a moving target: evolution of a treatment paradigm for atypical meningiomas amid changing diagnostic criteria. *Neurosurg Focus* 2008, 24:E3.
428. Pecchioli Z. Storia di un fungo della duramadre operato coll'estirpazione dal Professore Zanobi Pecchioli. *Nuovo Giornale dei Letterati-Scienze, Pisa* 1838, 36:39-44.
429. Pedal WP, Warzok RW, Hufnagl P, Roth K. Nucleolar organizer regions (AgNORs) in astrocytic tumors. *Zentralblatt Pathol* 1994, 140(1):89-94.
430. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)* 2015, 157(10):1683-1696.
431. Penfield WG. Cranial and intracranial endotheliomata - hemicraniosis. *Surg Gynecol Obstet* 1923, 36:657-674.

432. Perciaccante A, Cucu AI, Coralli A, et al. Mid-19th century Chinese medical portraits depict late-stage female breast tumours. *Lancet Oncology* 2019, 20(10):1347-1348.
433. Percy AK. Neoplasms of the central nervous system: epidemiologic considerations. *Neurology* 1970, 20: 398-399.
434. Perry A, Louis D, Scheithauer B, Budka H, Von Deimling A. *Meningiomas.* In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds). WHO *Classification of Tumors of the Central Nervous System*. Lyon: IARC Press, 2007.
435. Peschillo S, Delfini R. Trigeminal neuralgia: a new neuroimaging perspective. *World Neurosurg* 2013; 80:293-295.
436. Petit JL. Mem. Acad. R. Soc. Paris, 1718.
437. Phemister DB. The nature of cranial hyperostosis overlying endothelioma of the meninges. *Arch Surg* 1923, 6:554-572.
438. Pich A, Chiusa L. Margaria E. Prognostic relevance of AgNORs in tumor pathology. *Micron* 2000, 31(2):133-141.
439. Pieper DR, Al-Mefty O, Hanada Y, Buechner D. Hyperostosis associated with meningioma of the cranial base: secondary changes or tumor invasion. *Neurosurgery* 1999, 44:742-746, discussion: 746-747.
440. Ploton D, Visseaux - Coletto B, Canellas JC, et al. Semiautomatic quantification of silver - stained nucleolar organizer regions in tissue sections and cellular smears. *Anal Quant Cytol Histol Cytology* 1992, 14(1):14-23.
441. Pokhrel PK, Loftus SA. Ocular emergencies. *Am Fam Physician* 2007, 76:829-836.
442. Polyak S. The vertebrate visual system. Chicago: University Chicago Press, 1957.
443. Pornpanich K, Chindasub P. Eyelid tumors in Siriraj Hospital from 2000–2004. *J Med Assoc Thai* 2005, 88(Suppl 9): S11–S14.
444. Posner JB, Chernik, NL. Intracranial metastases from systemic cancer. *Adv Neurol* 1978, 19, 579-592.
445. Pradilla G, Jallo G. Arachnoid cysts: case series and review of the literature. *Neurosurg Focus* 2007, 22(2):E7.
446. Prestigiacomo CJ, Dagi TF. The history of skull base surgery. Neurosurg Focus 2012, 33(2):1-2.
447. Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst* 2002, 94(20):1555-1563.
448. Preston RA, Hirsh MM, Oster MD Jr, Oster HM. University of Miami Division of Clinical Pharmacology therapeutic rounds: drug-induced hyperkalemia. *Am J Ther* 1998, 5:125-132.
449. Prioreschi P. A *History of Medicine. Renaissance Medicine*, vol. 6. Omaha: Horatius Press, 2007.
450. Prioreschi P. *A history of medicine: Medieval medicine,* vol. 5. Omaha: Horatius Press, 2003.
451. Prioreschi P. *A History of Medicine: Primitive and Ancient Medicine*. Omaha: Horatius Press, 1996.

452. Prud'homme M, Mathieu F, Marcotte N, Cottin S. A pilot placebo controlled randomized trial of dexamethasone for chronic subdural hematoma. *Can J Neurol Sci* 2016, 43(2):284-290.
453. Rae ASL. The form and structure of the human claustrum. *J Comp Neurol* 1954, 100:15-39.
454. Rajendra S, Reeka P, Xu J, You C. Arachnoid cyst complicated by spontaneous chronic subdural hematoma in the infant. *Rom Neurosurg* 2012, 19:1.
455. Rao S, Sadiya N, Doraiswami S, Prathiba D. Characterization of morphologically benign biologically aggressive meningiomas. *Neurol India* 2009, 57(6):744–748.
456. Reil JC. Mangel des mittleren und freyen Teils des Balken im Menschengehirn. *Arch Physiol* 1812, 11:341-344.
457. Reil JC. Untersuchungen über den Bau des grossen Gehirns im Menschen. *Arch Physiol* 1809a, 9:136-208.
458. Reil JC. Die Sylvische Grube oder der Thal, das gestreifte grosse Hirngan-glium, dessen Kapsel und die Seitentheile des grossen Gehirns. *Arch Physiol* 1809b, 9:196.
459. Reil JC. Die vördere Commissur im grossen Gehirn. *Arch. Physiol* 1809c, 11:93.
460. Rengachary SS. Parasagittal arachnoid cyst: a case report. *Neurosurgery* 1981, 9:70-75.
461. Rengachary SS, Watanabe I. Ultrastructure and pathogenesis of intracranial arachnoid cysts. *J Neuropathol Exp Neurol* 1981, 40(1):61-83.
462. Rennert RC, Khan U, Tatter SB, et al. Patterns of clinical use of stereotactic laser ablation: analysis of a multicenter prospective registry. *World Neurosurg* 2018, 116:e566–e570.
463. Reynbakh O, Akhrass P, Souvaliotis N, et al. Use of MPH hemostatic powder for electrophysiology device implantation reduces postoperative rates of pocket hematoma and infection. *Curr Med Res Opin* 2018, 34(10):1861-1867.
464. Rhoton AL Jr. The lateral and third ventricles. *Neurosurgery* 2002, 51:207-271.
465. Ricalde P, Magliocca KR, Lee JS. Craniofacial fibrous dysplasia. *Oral Maxillofac Surg Clin North Am* 2012, 24:427-441.
466. Rich A. *A Dictionary of Roman and Greek Antiquities: with Nearly 2000 Engravings on Wood from Ancient Originals Illustrative of the Industrial Arts and Social Life of the Greeks and Romans.* London: Longmans, Green, 1860.
467. Riddle J. *Goddesses, Elixirs, and Witches: Plants and Sexuality Throughout Human History*. New York: Springer; 2010.
468. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol* 2008, 58(5 Suppl 2):S129-S132.
469. Ringel F, Cedzich C, Schramm J. Microsurgical technique and results of a series of 63 spheno-orbital meningiomas. *Neurosurgery* 2007, 60 (ONS Suppl 2):214-222.
470. Robinson A. Cunningham's Textbook of Anatomy. 5th Ed. New York: William Wood and Company, 1918.
471. Rogers L. Meningiomas in Pharaoh's people; hyperostosis in ancient Egyptian skulls. *Br J Surg* 1949, 36:423-424.

472. Roh JL, Sung MW, Kim KH, et al. Nasopharyngeal carcinoma with skull base invasion: a necessity of staging subdivision. *Am J Otolaryngol* 2004, 25:26-32.
473. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013, 9:231-236.
474. Roser F, Samii M, Ostertag H, et al. The Ki-67 proliferation antigen in meningiomas. Experience in 600 cases. *Acta Neurochir (Wien)* 2004, 146(1):37-44, discussion 44.
475. Rubiano AM, Carney N, Chesnut R, Puyana JC. Global neurotrauma research challenges and opportunities. *Nature* 2015, 527:S193-197.
476. Rubinstein AB, Shalit MN, Cohen ML, et al. Radiation- induced cerebral meningioma: a recognizable entity. *J Neurosurg* 1984, 61:966-971.
477. Rucker CW. The concept of a semi-decussation of the optic nerves. *AMA Arch Ophthalmol* 1958, 59:159-171.
478. Sadamori N, Shibata S, Mine M, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. *Int J Cancer* 1996, 67:318-322.
479. Sade B, Chahlavi A, Krishnaney A, et al. World Health Organization Grades II and III meningiomas are rare in the cranial base and spine. *Neurosurgery* 2007, 61(6):1194-1198.
480. Salem M, Wagih M, Badawy M. Study of Ki-67 expression and DNA ploidy in various grades of meningioma. *Egypt J Pathol* 2012, 32(2):211-216.
481. Salovey P, Rodin J. Some antecedents and consequences of social-comparison jealousy. *J Pers Soc Psychol* 1984, 47(4):780-792.
482. Salzmann J. Tumor capitis a carne fungosa productus & cum carie crania notabili conjunctus. *Acta Physico-Medica Academiae Caesareae Leopoldino-Carolinae Naturae Curiosum* 1730a, 2:225-228.
483. Salzmann J. Exostosisseu Ex crescentia Cranii osseospongiosa. *Acta Physico-Medica Academiae Caesareae Leopoldino-Carolinae Naturae Curiosum* 1730b, 2: 222-225.
484. Sandberg DI, Edgar MA, Resch L, et al. MIB-1 staining index of pediatric meningiomas. *Neurosurgery* 2001, 48(3):590-595, discussion 595-597.
485. Sankar T, Assina R, Karis JP, Theodore N, Preul MC. Neurosurgical implications of mannitol accumulation within meningioma and its peritumoral region demonstrated by magnetic resonance spectroscopy: case report. *J Neurosurg* 2008, 108(5):1010-1013.
486. Sansregret A, Ledoux R, Duplantis F, et al. Suprasellar subarachnoid cysts: radioclinical features. *Am J Roentgenol Radium Ther Nucl Med 1969*, 105:291-297.
487. Sarkies N. Traumatic optic neuropathy. *Eye* 2004, 18:1122-1125.
488. Sarton G. *Introduction to the history of science,* Vol. 2. Baltimore: Williams&Wilkins, 1927-1948.
489. Sawaya R. *Intracranial metastasis: Current Management Strategies*. Elmford: Blackwell/Futura, 2004.
490. Scarfo GB, Mariottini A, Palma L. Oculocerebral perforating trauma by foreign objects: diagnosis and surgery. *J Neurosurg Sci* 1990, 34:111-116.
491. Scatliff JH, Clark JK. How the brain got its names and numbers. *AJNR Am J Neuroradiol* 1992, 13(1):241-248.

492. Schmahmann JD, Pandya DN. *Fiber Pathways of the Brain*. New York: Oxford University Press, 2009.
493. Scholz M, Parvin R, Thissen J, et al. Skull base approaches in neurosurgery. *Head Neck Oncol* 2010, 2:16.
494. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. *Proc Natl Acad Sci USA* 1992, 89:5152-5156.
495. Shanafelt T, Dyrbye L. Oncologist burnout: causes, consequences, and responses. *J Clin Oncol* 2012, 30:1235-1241.
496. Shanafelt TD, Balch CM, Bechamps GJ, et al. Burnout and career satisfaction among American surgeons. *Ann Surg* 2009, 250:463-471.
497. Sharifi G, Jalessi M, Erfanian D, Farhadi M. Sudden blindness due to isolated sphenoid sinus mucocele and retention cyst. *Braz J Otorhinolaryngol* 2013, 79:120.
498. Sharma HS, Zimmermann-Meinzingen S, Johanson CE. Cerebrolysin reduces blood cerebrospinal fluid barrier permeability change, brain pathology, and functional deficits following traumatic brain injury in the rat. *Ann NY Acad Sci* 2010, 1199:125-137.
499. Sharma D, Mathur PN, Saini OP. Ocular Injury & its medico legal implications. *J Indian Acad Forensic Med* 2008, 30:227-230.
500. Shawkat HS, Westwood M, Mortimer A. Mannitol: a review of its clinical uses. *Continuing Education in Anaesthesia Critical Care & Pain* 2012, 12:82-85.
501. Shields JA, Shields CL. Intraocular tumors: an atlas and textbook. 2nd edition, Philadelphia: Lippincott Williams & Wilkins, 2008.
502. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. *Ophthalmology* 2004, 111(5):997-1008.
503. Shin RK, Qureshi RA, Harris NR, et al. Wilbrand knee. *Neurology* 2014, 82:459-460.
504. Shintani T, Hayakawa N, Hoshi M, et al. High incidence of meningioma among Hiroshima atomic bomb survivors. *J Radiat Res (Tokyo)* 1990, 40:49-57
505. Shoshan Y, Chernova O, Juen SS, et al. Radiation-induced meningioma: a distinct molecular genetic pattern? *J Neuropathol Exp Neurol* 2000, 59:614-620.
506. Shrivastava RK, Sen C, Costantino PD, Della Rocca R. Sphenoorbital meningiomas: surgical limitations and lessons learned in their long-term management. *J Neurosurg* 2005, 103:491-497.
507. Sidhu GS, Ghag A, Prokuski V, et al. Civilian gunshot injuries of the spinal cord: a systematic review of the current literature. *Clin Orthop Relat Res* 2013, 471(12):3945-3955.
508. Simis A, Pires de Aguiar PH, Leite CC, et al. Peritumoral brain edema in benign meningiomas: correlation with clinical, radiologic, and surgical factors and possible role on recurrence. *Surg Neurol* 2008, 70(5):471-477.
509. Simpson DA, Crompton JL. The visual fields: an interdisciplinary history I. The evolution of knowledge. *J Clin Neurosci* 2008, 15:101-110.
510. Sindou M, Howeidy T, Acevedo G. Anatomical observations during microvascular decompression for idiopathic trigeminal neuralgia (with correlations between

topography of pain and site of the neurovascular conflict): prospective study in a series of 579 patients. *Acta Neurochir* 2002a, 144:1-12.

511. Sindou M, Leston J, Decullier E, Chapuis F. Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. *J Neurosurg* 2002b, 107:1144-1153.
512. Sindwani R. Use of novel hemostatic powder MPH for endoscopic sinus surgery: initial impressions. *Otolaryngol Head Neck Surg* 2009, 140(2):262-263.
513. Singh A, Samuel H. Selesnick SH. *Meningiomas of the posterior fossa and skull base* In: Jackler RK, Braekmann DF (eds). *Neurology.* 2th ed., Philadelphia: Elsevier Mosby, 2005.
514. Singh P, Misra GS, Singh A, Murthy MGK. Missile injuries of brain - an experience in Northern Sector. *Med J Armed Forces India* 2003, 59:290-297.
515. Smely C, Orszagh M. Intracranial transorbital injury by a wooden foreign body: re-evaluation of CT and MRI findings. *Br J Neurosurg* 1999, 13:206-211.
516. Smith CMU. *Understanding the nervous system in the 18th century*. In: Finger S, Boller F, Tyler KL (eds). *Handbook of Clinical Neurology. History of Neurology*. Vol. 95. Amsterdam: Elsevier, 2010.
517. Smith WW, Finkelstein N, Smith HW. Renal excretion of hexitols (sorbitol, mannitol, and dulcitol) and their derivatives (sorbitan, isomannide, and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J Biol Chem* 1940, 135:231-250.
518. Smith W. *A Dictionary of Greek and Roman Antiquities,* second ed. Boston: Little Brown and Company, 1859.
519. Smith W, Anthon C. *A Dictionary of Greek and Roman Antiquities.* New York: Harper & Brothers, 1857.
520. Smith W. *A Dictionary of Greek and Roman Antiquities*. 2nd Ed. London: Walton & Maberly, 1853.
521. Smith W, Anthon C. *A School Dictionary of Greek and Roman Antiquities: Abridged from the Larger Dictionary.* Michigan: University of Michigan Library (1846/2005).
522. Smith W, Anthon C. *A Dictionary of Greek and Roman Antiquities.* New York: American Book Company, 1843.
523. Sobotta J. Atlas and textbook of human anatomy, Philadelphia: Saunders, 1909.
524. Soffer D, Pittaluga S, Feiner M, Beller AJ. Intracranial meningiomas following low-dose irradiation to the head. *J Neurosurg* 1983, 59:1048-1053.
525. Soleman J, Noccera F, Mariani L. The conservative and pharmacological management of chronic subdural haematoma: a systematic review. *Swiss Med Wkly* 2017, 147:1-9.
526. Sorani MD, Morabito D, Rosenthal G, et al. Characterizing the dose-response relationship between mannitol and intracranial pressure in traumatic brain injury patients using a high-frequency physiological data collection system. *J Neurotrauma* 2008, 25(4):291-298.
527. Spiller WG. A case of Jacksonian epilepsy with hemianopsia and monohypertonia, and a case of hemihypertonia post-epileptica. *Trans Coll Phys Phila* 1899, 21:191.

528. Spraul CW, Ahr WM, Lang GK. Clinical and histologic features of 141 primary basal cell carcinomas of the periocular region and their rate of recurrence after surgical excision. *Klin Monbl Augenheilkd* 2000, 217(4):207-214.
529. Steinke H. *Irritating Experiments: Haller's Concept and the European Controversy on Irritability and Sensibility, 1750-90*. Amsterdam: Rodopi, 2005.
530. Suarez C, Llorente JL, Fernandez De Leon R, et al. Prognostic factors in sinonasal tumors involving the anterior skull base. *Head Neck* 2004, 26(2):136-144.
531. Sun TF, Boet R, Poon WS. Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. *Br J Neurosurg* 2005, 19(4): 327-333.
532. Swanson L. *Neuroanatomical terminology: a lexicon of classical origins and historical foundation.* New York: Oxford University Press, 2014.
533. Tabareau-Delalande F, Collin C, Gomez-Brouchet A, et al. Diagnostic value of investigating GNAS mutations in fibro-osseous lesions: a retrospective study of 91 cases of fibrous dysplasia and 40 other fibro-osseous lesions. *Mod Pathol* 2013, 26: 911-921.
534. Tabouret E, Chinot O, Metellus P, et al. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res* 2012, 32:4655-4662.
535. Tailor TD, Gupta D, Dalley RW, et al. Orbital neoplasms in adults: clinical, radiologic, and pathologic review. *Radiographics* 2013, 33(6):1739-58.
536. Takano T, Uno M, Yamano T, Shimada M. Congenital hydrocephalus: role of transplacental myxovirus infection. *Congenit Anom (Kyoto)* 1995, 35(1):15-24.
537. Talacchi A, Corsini F, Gerosa M. Hyperostosing meningiomas of the cranial vault with and without tumor mass. *Acta Neurochir (Wien)* 2011, 153:53-61.
538. Tamas I, Tamas C, Enasoae I, Turliuc D. Illness and healing in the Holy Scripture. Church serving the elderly and sick: bioethics for care people suffering from neuro-degenerative diseases, primary and metastatic brain tumors. *Romanian Journal of Bioethics* 2015, 13(3):1-11.
539. Tan SR, Tope WD. Effectiveness of microporous polysaccharide hemospheres for achieving hemostasis in Mohs micrographic surgery. *Dermatol Surg* 2004, 30(6): 908-914.
540. Tao X, Dong J, Hou Z, et al. Clinical features, treatment, and prognostic factors of 56 intracranial and intraspinal clear cell meningiomas. *World Neurosurg* 2018, 111:e880-e887.
541. Tesluk GC. Eyelid lesions: incidence and comparison of benign and malignant lesions. *Ann Ophthalmol* 1985, 17(11):704-707.
542. Theuer SE, Krayenbühl N, Scheffel H, et al. Metastases in Meckel's Cave. A Challenge of Differential Diagnosis. *Clin Neuroradiol* 2007, 17:41-47.
543. Thotakura AK, Marabathina NR. Nonsurgical treatment of chronic subdural hematoma with steroids. *World Neurosurgery* 2015, 84(6):1968-1972.
544. Tingerides C, Uttley A, Minks D, Exley C. *First FRCR Anatomy: Practice Cases*. London: J.P. Medical, 2013.

545. Tisher RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys* 1993, 27(2):215-221.
546. Todd NV. Priapism in acute spinal cord injury. *Spinal Cord* 2011, 49(10):1033-1035.
547. Tokiyoshi K, Yoshimine T, Maruno M, et al. The analysis of nuclear organizer regions of astrocytomas with various histologic malignancies. *No To Shinkei-Brain and Nerve* 1992, 44(12):1083-1086.
548. Tokunaga Y, Khalid H, Hiura T, Shibata S. Proliferation of Human Intracranial Neoplasm Assessed with Ki-67 (MIB-1) Labeling Index and Argirophilic Nucleolar Organizer Regions. *Acta Med Nagasaki* 1997, 42:44-50.
549. Tomita T, Kurimoto M, Yamatani K, et al. Multiple meningiomas consisting of fibrous meningioma and anaplastic meningioma, *J Clin Neurosci* 2003, 10:622-624.
550. Traynor JE, Casey HW. Five-year follow-up of primates exposed to 55 MeV protons. *Radiat Res* 1971, 47: 143-148
551. Trerè D. AgNOR staining and quantification. *Micron* 2000, 31(2):127-131.
552. Troupp H, Valtonen S, Vapalahti M. Intraventricular pressure after administration of dehydrating agents to severely brain-injured patients: is there a rebound phenomenon? *Acta Neurochirurgica* 1971, 24:89-95.
553. Tschan CA, Nie M, Schwandt E, Oertel J, Safety and efficacy of microporous polysaccharide hemospheres in neurosurgery. *Neurosurgery* 2011, 69(1 Suppl Operative):ons49-63.
554. Tsermoulas G, Turel MK, Wilcox JT, et al. Management of multiple meningiomas. *J Neurosurg* 2018, 128(5):1403-1409.
555. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer* 1983, 52:2349-2354.
556. Tubbs RS. Anatomy. The oldest child of Mother Medicine. *Clin Anat* 2014, 27(6):805.
557. Tubbs RS, Loukas M, Shoja MM, et al. Costanzo Varolio (Constantius Varolius 1543-1575) and the Pons Varolli. *Neurosurgery* 2008, 62(3):734-737.
558. Tufano A, Guida A, Coppola A, et al. Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. *Blood Transfus* 2013, 6:1-6.
559. Turbin RE, Maxwell DN, Langer PD, et al. Patterns of transorbital intracranial injury: a review and comparison of occult and non-occult cases. *Surv Ophthalmol* 2006, 51:449-460.
560. Turliuc MD, Cucu AI, Costachescu B, et al. The use of mannitol in neurosurgery and neuro-ophthalmology. *Cell Chem Technol* 2019, 53 (7-8): 625-633.
561. Turliuc MD, Cucu AI, Perciaccante A, et al. Hydrocephalus of King Charles II of Spain, the Bewitched King. *European Neurology* 2019a, 81(1-22):76-78.
562. Turliuc MD, Cucu AI, Carauleanu A, Costea CF. Efficiency and safety of microporous polysaccharide hemispheres from potato starch in brain surgery. *Cell Chem Technol* 2018, 52 (7-8): 505-513.
563. Turliuc MD, Turliuc S, Cucu AI, et al. Through clinical observation: the history of priapism after spinal cord injuries. *World Neurosurgery* 2018a, 109:365-371.
564. Turliuc DM, Costea CF, Turliuc S, et al. The lion heart of a neurosurgeon: the stress during a life of neurosurgery. *Romanian Neurosurgery* 2018b, 32(2): 211-216.

565. Turliuc DM, Cucu AI, Arbore-Sorete R, et al. Orbitocranial penetrating injury by a metallic foreign body. Case report and anatomical considerations. *Romanian Neurosurgery* 2017, 31(4):437-443.
566. Turliuc D, Turliuc S, Cucu A, et al. An entire universe of the Roman world's architecture found in the human skull. *Journal of History of the Neurosciences* 2017a, 26(1):88-100.
567. Turliuc DM, Costachescu B, Poeata I, et al. Late diagnosed PHACE syndrome by aneurysmal subarachnoid hemorrhage. Case report. *Rev Med Chir Soc Med Nat Iasi* 2017b, 121(3): 562-567.
568. Turliuc DM, Cucu AI, Costan VV, Costea CF. Rare etiology of trigeminal nerve neuralgia – metastatic adenocarcinoma of the colon. *Romanian Journal of Oral Rehabilitation* 2016, 8(2): 40-43.
569. Turliuc DM, Cucu AI, Dobrovăț B, et al. A rare case of suprasellar arachnoid cyst with giant perimesencephalic and mesial temporal extension- physiopathological mechanisms. *Romanian Neurosurgery* 2016a, 30(1): 52-56.
570. Turliuc DM, Cucu AI, Costea CF. 3 years long-term posttraumatic cerebrospinal fluid fistula complicated with recurrent meningitis. *Romanian Journal of Oral Rehabilitation* 2016b, 8(4):95-99.
571. Turliuc DM, Sava A, Cucu AI, et al. Cribriform plate and Galen's cribrum romanum. *Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology* 2016c, 15(1):123-126.
572. Turliuc D, Trandafir D, Cucu A, et al. Giant nasopharingeal carcinoma – a case report. Dynamic anatomical models in skull base and intracranial space invasion. *Romanian Journal of Oral Rehabilitation* 2016d, 8(1):51-58.
573. Turliuc DM, Turliuc S, Cucu AI, et al. An unwritten anatomy lesson: the influence of roman clothing on neuroanatomical terminology: in memoriam Albert L. Rhoton, Jr. (1932–2016). *Clinical Anatomy* 2016e, 29:680-690.
574. Turliuc D, Turliuc S, Cucu A, et al. A review of analogies between some neuroanatomical terms and roman household objects. *Annals of Anatomy* 2016f, 204:127-133.
575. Turliuc D, Dobrovat B, Cucu A, et al. To be or not to be a neurovascular conflict: importance of the preoperative identification of the neurovascular conflict in the trigeminal neuralgia. *Romanian Neurosurgery* 2016g, 30 (3):334-341.
576. Turliuc DM, Turliuc S, Cucu AI, Costea CF. Professional envy among doctors. *Romanian Journal of Oral Rehabilitation* 2016h, 8(3):80-85**.**
577. Turliuc S, Costea CF, Cucu AI, Dumitrescu AM, et al. Biblical descriptions of spinal neurological and neurosurgical pathology. *Romanian Neurosurgery* 2016i, 30(3):360-365.
578. Turliuc D, Sava A, Dumitrescu GF, et al. Right visual loss due to choroidal metastasis of a papillary adenocarcinoma of the lung, Case report. *Rom J Morphol Embryol* 2015, 56(3): 1173-1177.

579. Turliuc DM, Costan VV, Cucu AI, Costea CF. Intraorbital Foreign Body. *Revista Medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi* 2015a, 119(1):179-184.
580. Turliuc D, Turliuc S, Mihailov I, et al. Homicide by cervical spinal cord gunshot injury with shotgun fire pellets: case report. *International Journal of Medical Research & Health Sciences* 2015b, 4(4): 928-931.
581. Turliuc MN, Mairean C, Turliuc MD. Rumination and supression as mediators of the relationship between dysfunctional beliefs and traumatic stress. *International Journal of Stress Management* 2015c, 22(3):306-322.
582. Turliuc D, Turliuc S, Cucu A, et al. Claiming dignity while dangling between life and death. *Romanian Journal of Artistic Creativity* 2015d, 3(1):34-38.
583. Turliuc D, Sorete Arbore R, Dobrin N, et al. Subarachnoid hemorrhage in a young patient with a factor V Leiden thrombophilia: case report and literature review. *Romanian Neurosurgery* 2013, 20(2): 170-179.
584. Turliuc D, Cucu A. Management of mild, and moderate head injuries in adults. *Romanian Neurosurgery* 2010, 17(4):421-431.
585. Turliuc D, Dumitrescu GF, Indrei A. Colaborarea neurochirurg-neuropatolog in diagnosticarea tumorilor cerebrale. *Rev Med Chir Soc Med Nat Iasi* 2007, 3 (3): 649-657.
586. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science* 1974, 185:1124-1131.
587. Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol* 2005, 24(4 Suppl):S57-S62.
588. Uzüm N, Ataoğlu GA. Histopathological parameters with Ki-67 and bcl-2 in the prognosis of meningiomas according to WHO 2000 classification. *Tumori* 2008, 94(3):389–397
589. Van Gelderen BR, Bakker AB, Konijn EA, Demerouti E. Daily suppression of discrete emotions during the work of police service workers and criminal investigation officers. *Anxiety, Stress & Coping: An International Journal* 2011, 24:515-537.
590. Vater A, Heinicke JC. *Dissertatio, qua visus vitia duo rarissima, alterum duplicati, alterum dimidiati physiologice & pathologice considerata exponuntur*. In: Haller A (ed) *Disputationes ad morborum historiam et curationem facientes*. Lausanne: M. M. Bousquet et soc, 1757.
591. Venes D. *Taber's Cyclopedic Medical Dictionary*, twenty-second ed. Philadelphia: Davis F. A. Company, 2013.
592. Vergani F, Morris CM, Mitchell P, Duffau H. Raymond de Vieussens and his contribution to the study of white matter anatomy: Historical vignette. *Journal of Neurosurgery*, 117, 1070-1075, 2012.
593. Verhoeven V, Vrints I, De Keyser J, et al. A contemporary and a historical patient with an ectopic meningioma. *Acta Chir Belg* 2019, 119(4):254-258.
594. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007, 357:1821-1828.

595. Vesalius A, Richardso WF, Carman JB. *On the Fabric of the Human Body. Book VI: The Heart and Associated Organs, Book VII: The Brain, a translation of De Humani Corporis Fabrica Libri Septem.* Novato: Jeremy Norman Co., 1543/2009.
596. Vesalius A. *De Humani Corporis Fabrica Libri Septem*. Basel: Joannis Oporinus, 1543.
597. Vialou D. *La Préhistoire.* Paris: Gallimard, 1991.
598. Vicq D'Azyr F. *Traité d'Anatomie et de Physiologie avec des planches coloriées représentant au naturel les divers organes de l'Homme et des animaux, vol 1. Anatomie du cerveau*. Paris: Amb Didot l'aîné, 1786.
599. Vieussens R. *Neurographia Universalis*. Lyons: Lugduni, Apud Joannem Certe, 1685.
600. Vikram B, Chu FCH. Radiation therapy for metastases to the base of the skull. *Radiology* 1979, 130(2):465-468.
601. Virchow R. *Die krankhaften Geschwülste.* Berlin: A. Hirschwald, 1864.
602. Von Graefe A. Ueber die Untersuchung des Gesichtsfeldes bei amblyopischen Affectionen. *Graefes Arch Ophthalmol* 1856, 2:258-298.
603. Von Haller A. De partibus corporis humani sensibilibus et irritatebilibus. *Bull Hist Med* 1936, 4:651-699.
604. Von Haller A. *Elementa Physiologiae Corporis Humani.* Lausannae: Sumptibus M. M. Bousquet et Sociorum, 1757-1766.
605. Vries J, Wakhloo AK. Cerebral oedema associated with WHO-I, WHO-II, WHO-III meningiomas: correlation of clinical, computed tomography, operative and histological findings. *Acta Neurochir (Wien)* 1993, 125:34-40.
606. Wade NJ. *A natural history of vision,* vol 13. Cambridge: MIT Press, 1999.
607. Wade TR, Ackerman AB. The many faces of basal-cell carcinoma. *J Dermatol Surg Oncol* 1978, 4(1):23-28.
608. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev 2007,* 24(1):CD001049.
609. Walsh JJ. *The Popes and science: The history of the papal relations to science during the middle ages and down to our own time*. New York: Fordham University Press, 1915.
610. Wang XQ, Huang MZ, Zhang H, et al. Clear cell meningioma: clinical features, CT, and MR imaging findings in 23 patients. *J. Comput Assist Tomo* 2014, 38(2):200-208.
611. Wang R, Mao M. MRI findings of NPC invasion in skull base. *Chin Med Image Tech* 2001, 17:428-429.
612. Waters RL, Hu SS. *Penetrating injuries of the spinal cord stab and gunshot injuries*. In: Frymoyer JW (eds). *The adult spine: principles and practice*. New-York: Raven Press, 1991.
613. Weber F, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 2006, 240:81-84.
614. Weber J, Spring A, Czarnetzki A. Parasagittales Meningeom bei einem 32.500 Jahrealten Schädel aus dem Südwesten von Deutschland: Neue Erkenntnisseüber den Umgangmit Krankheit in der Altsteinzeit. *Deut Med Wochenschr* 2002, 127:2757-2760.
615. Weinstein LS, Chen M, Liu J. Gs (alpha) mutations and imprinting defects in human disease. *Ann NY Acad Sci* 2002, 968:173-197.

616. Weisz GM (1997). The papal contribution to the development of modern medicine. *Australian and New Zealand Journal of Surgery* 1997, 67, 472-475.
617. Wellisch DK, Kelita TA, Freeman D. Predicting major depression in brain tumor patients. *Psychooncology* 2002, 11(3):230-238.
618. Wester K. Gender distribution and sidedness of middle fossa arachnoid cysts: a review of cases diagnosed with computed imaging. *Neurosurgery* 1992, 31:940-944.
619. Westfall RS. Varolio, Costanzo in The Galileo Project. http://galileo.rice.edu/Catal og/NewFiles/varol io.html, 1995.
620. White KD. *Farm Equipment of the Roman World*. Cambridge: Cambridge University Press, 1975.
621. Whittaker CR. *Frontiers of the Roman Empire: A Social and Economic Study*. Baltimore: Johns Hopkins University Press, 1997.
622. Wickens AP. *A History of the Brain: From Stone Age Surgery to Modern Neuroscience*. New York: Psychology Press, 2015.
623. Wilbrand H. Schema des Verlaufs der Sehnervenfasern durch das Chiasma. *Z Augenheilkd* 1926, 59:135-144.
624. Wilkins RH. *Neurosurgical Classics*. New York: Thieme, 1992.
625. Wilkinson J, The case of the bent woman in Luke 13: 10-17, *Biblical Studies*, UK, p 195-205
626. Willis J, Smith C, Ironside JW, et al. The accuracy of meningioma grading: a 10-year retrospective audit. *Neuropathol Appl Neurobiol* 2005, 31:141-149.
627. Winslow JB. *Exposition Anatomique de la Structure du Corps Humain*. Paris: Desprez-Desessartz, 1732.
628. Wolpoff M. *Paleoanthropology*. Boston: McGraw-Hill, 1999.
629. Wong RH, Wong AK, Vick N, et al. Natural history of multiple meningiomas. *Surg Neurol Int* 2013, 4:71.
630. Wong SW, Smith R, Crowe P. Optimizing the operating theatre environment. *ANZ J Surg* 2010, 80:917-924.
631. Wong GK, Zhu XL, Poon WS. Beneficial effect of Cerebrolysin on moderate and severe head injury patients: result of a cohort study. *Acta Neurochir Suppl* 2005, 95:59-60.
632. Wright J. The Nose and throat in medical history. *The Laryngoscope* 1902, 12: 260-280.
633. Wu A, Sun MT, Huilgol SC, et al. Histological subtypes of periocular basal cell carcinoma. *Clin Exp Ophthalmol* 2014, 42(7):603-607.
634. Wu H. History and current situation of lateral skull base surgery. *Shanghai Commun Univ J* 2007, 27:1-5.
635. Y Cajal SR. *Histologie du Système Nerveux de l'Homme et des Vértèbres*. Paris: Maloine, 1911.
636. Y Cajal SR. *Textura del Sistema Nervioso del Hombre y de los Vertebrados*, vol 1., Madrid: Moya, 1899.
637. Yadav VK, Ducy P. Lrp5 and bone formation: a serotonin dependent pathway. *Ann NY Acad Sci* 2010, 1192:103-109.

638. Yilmazlar S, E. Arslan, H. Kocaeli, et al. Cerebrospinal fluid leakage complicating skull base fractures: analysis of 81 cases. *Neurosurg Rev* 2006, 29: 64-71.
639. York GK, Steinberg DA. *Neurology in Ancient Egypt*. In: Finger S, Boller F, Tyler KL (eds). *Handbook of Clinical Neurology*, Vol. 95. *History of Neurology*. Edinburgh: Elsevier, 2010.
640. Yoshida G, Garland D, Waters RL. Gunshot wounds to the spine. *Orthop Clin North Am* 1995, 26(1):109-116.
641. Yousry I, Camelio S, Schmid UD, et al. Visualization of cranial nerves I-XII: value of 3D CISS and T2-weighted FSE sequences. *Eur Radiol* 2000, 10:1061-1067.
642. Youssef KK, Van Keymeulen A, Lapouge G, et al. Identification of the cell lineage at the origin of basal cell carcinoma. *Nat Cell Biol* 2010, 12(3):299-305.
643. Zacharis C. *Lactitol*. In: O'Donnell K, Kearsley MW (eds) *Sweeteners and sugar alternatives in food technology*. West Sussex: Wiley-Blackwell, 2012.
644. Zaher A, Abdelbari Mattar M, Zayed DH, et al. Atypical meningioma: a study of prognostic factors. *World Neurosurg* 2013, 80(5):549-553.
645. Zakrzewska JM, Lopez BC, Kim SE, Coakham HB. Patients reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. *Neurosurg* 2005, 56:1304-1312.
646. Zhang Y, Chen S, Xiao Y, Tang W. Effects of dexamethasone in the treatment of recurrent chronic subdural hematoma. *World Neurosurgery* 2017, 105:115-121.
647. Zhang Y, Chopp M, Meng Y, et al. Improvement in functional recovery with administration of Cerebrolysin after experimental closed head injury. *J Neurosurg* 2013, 118: 1343-1355.
648. Ziegler R. Urmenschenfunde in Baden-Württemberg. *Stuttg Beitrg Naturk* 1999, C44:24-39.