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METHODS OF EVALUATION OF CLINICAL AND BIOCHEMICAL STATUS IN PATIENTS WITH CHRONIC OTITIS MEDIA WITH CHOLESTEATOMA

ABSTRACT OF THE PhD THESIS

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The PhD thesis contain a general part structured in 4 chapters, totaling 40 pages, a personal part consisting of 8 chapters, totaling 102 pages, 110 figures, 33 tables, 350 bibliographic references and an annex.

The contents and abbreviations are kept as they are found in the phd thesis and the figures and tables selected for the abstract keep the numbering within the thesis.

Keywords: chronic otitis media, cholesteatoma, oxidative stress, inflammation, quality of life.

CONTENTS

1. Study motivation

Chronic otitis media with cholesteatoma is a common pathology in otology, with unpredictable and progressive evolution that can cause many complications.

Recent studies focus on identifying pathologies determined by oxidative stress, which has been shown to be involved in many acute and chronic conditions. There are a limited number of studies that analyze the involvement of oxidative markers in CSOM determinism with and without cholesteatoma, some with contradictory results. It is also known that local and systemic inflammatory processes function as cofactors in the progression of some pathologies. The accumulation of ROS in tissues causes their deterioration, generates modifications of lipids, proteins and DNA, favoring cell death. Organisms, in order to protect themselves from the effects of these toxic products, have developed antioxidant systems such as SOD, CAT and glutathione peroxidase. When ROS are increased due to chronic inflammation, the antioxidant system activates to remove them from the tissues.

Inflammatory mediators play an important role in the pathogenesis of otitis media by initiating and maintaining an inflammatory response to the infection. The presence of inflammatory mediators could be one of the reasons why, in some patients, acute otitis media transforms into CSOM or cholesteatoma recurrence. The most important cytokines studied so far involved in otitis media pathology are IL-1, IL-4, Il-5, IL-6, IL-8, IL-10, IL-12, IL-13.

Another important aspect is the quality of life of patients with chronic ear conditions. The achievement of a normal quality of life has grown in the last decades due to the need to personalize the medical-surgical treatment. In most European countries there are instruments for quantifying the medical act through simple questionnaires, which can be completed by patients and / or by the patients caregivers. In Romania, there is currently no instrument for assessing the quality of life of patients with chronic ear conditions. By validating COMOT-15 and COMQ-12 questionnaires, a detailed assessment of the impact of the disease symptoms on work and lifestyle, on the degree of addressability to the specialized medical services as well as the general impact on the patient can be made.

2. The purpose of the research

The purpose of the present study is to investigate the involvement of oxidative stress markers and proinflammatory cytokines in CSOM pathology

with and without cholesteatoma, and in cholesteatoma recurrence, with the correlation between the obtained values.

The study also proposes a cultural adaptation and validation in Romanian of quality of life questionnaires, COMQ-12 and COMOT-15, specific for patients with chronic ear condition that can be applied in the health system and used for assessing the impact of the disease. They are widely used in Europe. The questionnaires applied to groups of patients will be analyzed and the results obtained will be used to optimize the medical and the surgical treatment.

3. Study 1: assessment of oxidative stress and inflammatory status of patients with chronic otitis media with cholesteatoma

3.1. Introduction

Throughout the enzymatic and non-enzymatic processes normally produced in a cell, O_2 accepts single electrons to form ROS (Papaharalambus et al, 2007). Cells are protected against ROS effects by repair processes, free radicals compartmentalization, defensive enzymes, endogenous and exogenous antioxidants (which identify and inactivate free radicals) (Mirończuk-Chodakowska et al, 2018). The SOD defense enzyme removes the superoxide free radical. CAT and glutathione peroxidase remove hydrogen peroxide and lipid peroxides. Vitamin E, vitamin C and plant flavonoids act as antioxidants (Voronkova et al, 2018). Thus oxidative stress can be defined as the increased production of ROS and NROS, which exceeds the ability of an organism to remove or neutralize them, by means of cellular defense mechanisms. Oxidative stress is an alteration of the balance between ROS and NROS production and the eliminatuon process (Voronkova et al, 2018).

3.2. Material and method

The prospective study was performed on a group of 60 patients aged between 9 and 58 years diagnosed with CSOM with and without cholesteatoma, admitted for surgery in Clinical Rehabilitation Hospital from Iasi. Of these 28 patients were with CSOM, 22 with CSOM with cholesteatoma and 11 with cholesteatoma recidivism. The criteria for inclusion in this study were: imaging and clinical diagnosis of CSOM, patient without other known acute or chronic pathologies and non-smoker or chronic alcohol consumer, agreement to participate in the study. The exclusion criteria were: the existence of an acute or chronic pathology, with the exception of the ear problems, chronic alcoholic consumer or smoker, following a drug treatment, including vitamin treatment.

We also collected demographic data such as age, sex and environment information, but also biological constants: erythrocytes (RBC), leukocytes (WBC), platelets (PLT), haematic sedimentation rate (VSH), C-reactive protein (CRP)), fibrinogen, urea, creatinine, uric acid, blood sugar and ear secretion.

The patients in the study group were divided into 4 groups: group M included healthy persons, group C grouped patients with CSOM with cholesteatoma, group R contained patients with relapse of cholesteatoma, and group O included patients with simple OMCS.

The markers of oxidative stress that were dosed were SOD, CAT, MDA and TAC. The inflammatory status was studied by dosing IL-1α, IL-6, IL-8.

3.3. Results

Skewness / Kurtosis tests (-2 <p <2) suggest that the TAC, SOD, MDA and CAT value ranges were homogeneous.

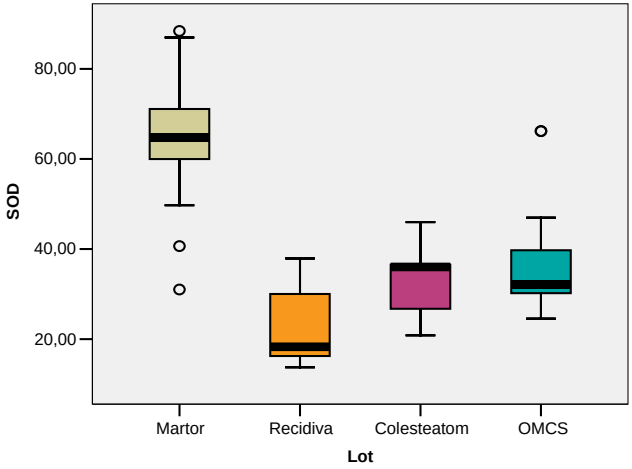

Fig. 21. *Mean SOD values compared to study groups*

In the group with cholesteastoma, the activity of SOD (inhibition rate%) ranged from 20,853 to 45,972, and in patients with CSOM the variation was between 24,562 and 66,173, registering the lowest average level in patients with cholesteatoma recidivism, followed by the one registered in patients with cholesteastoma, significantly lower compared to the control group (22,929;

32,541 (p = 0.004)). The mean level recorded in patients with cholesteastoma was slightly lower compared to the patients with CSOM, but significantly lower compared to the control group (32,541; 36,309 (p = 0,160) *vs* 64,475; p = 0.001) (Fig. 21).

In the groups with cholesteastoma CAT ranged from 1.253 mU / mL to 2.531 mU / mL and in the group with CSOM from 0.611 mU / mL to 2.461 mU / mL, registering significantly higher mean levels compared to the control group (1.737 mU / mL; 1.447 mU / mL (p = 0.05) *vs* 0.501 mU / mL; p = 0.001). The mean level recorded in patients with cholesteatoma recidivism was slightly lower compared to patients with cholesteatoma, but significantly higher compared to the control group (1.593 mU / mL; 1.737 mU / mL (p = 0.328) *vs* 0.501 mU / mL; p = 0.001) (Fig. 22).

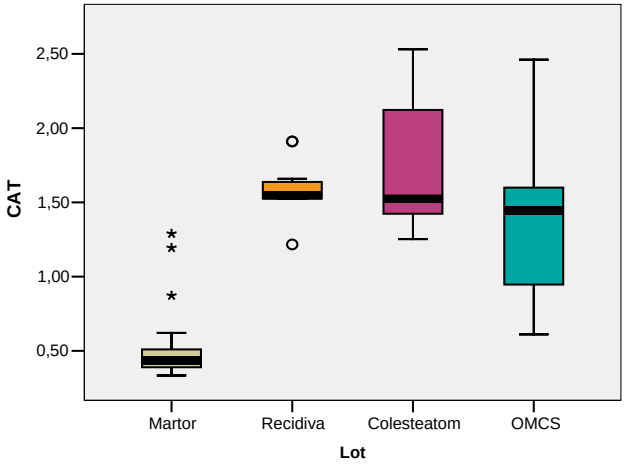

Fig.22. *Mean CAT values (mU / mL) compared to study groups*

In the cholesteatoma group, the MDA ranged from 0.715 nmol / µL to 1.15 nmol / µL, and in CSOM patients the variation ranged from 0.814 nmol / µL to 0.973 nmol / µL, with the lowest mean level in patients from the control group, significantly lower compared to the levels recorded in patients with cholesteatoma and CSOM (0.948 nmol / µL; 0.891 nmol / µL (p = 0.01) *vs* 0.625 nmol / µL; p = 0.001). The mean level recorded in patients with cholesteatoma recidivism was slightly higher compared to patients with cholesteatoma, but significantly higher compared to the control group (0.979 nmol / µL; 0.948 nmol / µL *vs* 0.625 nmol / µL; p = 0.001) (Fig. 23).

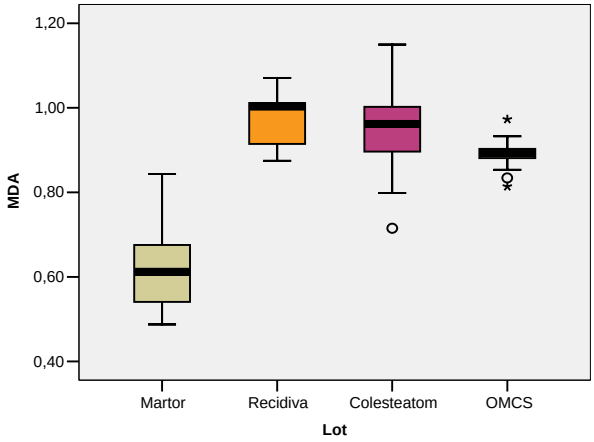

Fig.23. *Mean MDA values (nmol / µL) compared to study groups*

In groups with cholesteatoma, TAC ranged from 26.908 mmol / µL to 28.608 mmol / µL and in the one with CSOM from 25.815 mmol / µL to 39.313 mmol / µL, with significantly lower mean levels compared to the control (27.519 mmol/µL; 27.834 mmol / µL *vs* 29.401 mmol / µL; p = 0.001).

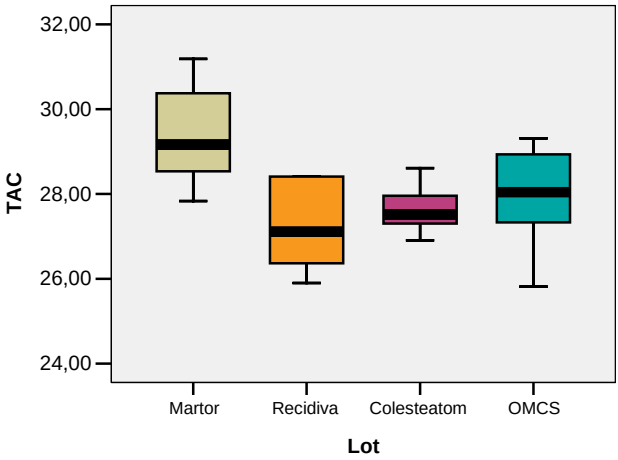

Fig.24. *Mean CT values (mmol / µL) compared to study groups*

The mean level recorded in patients with cholesteatoma recidivism was slightly lower compared to patients with cholesteatoma, but significantly lower compared to the control group (27,210 mmol / µL; 27.657 mmol / µL (p = 0.115) *vs* 29.401 mmol / µL; p = 0.001) (Fig. 24).

In groups with cholesteatoma, IL-1α ranged from 1.91 pg / ml to 3.52 pg / ml (Table XI) and in the one with CSOM from 1.81 pg / ml to 3.34 pg / ml, with significantly lower mean levels compared to patients with cholesteatoma recidivism (3.011 pg / ml; 2,911 pg / ml (p = 0.964) *vs* 5.021 pg / ml; p = 0.001). The mean level recorded in the control was significantly lower compared to the other analyzed groups (0.815 pg / ml; p = 0.001) (Fig.35).

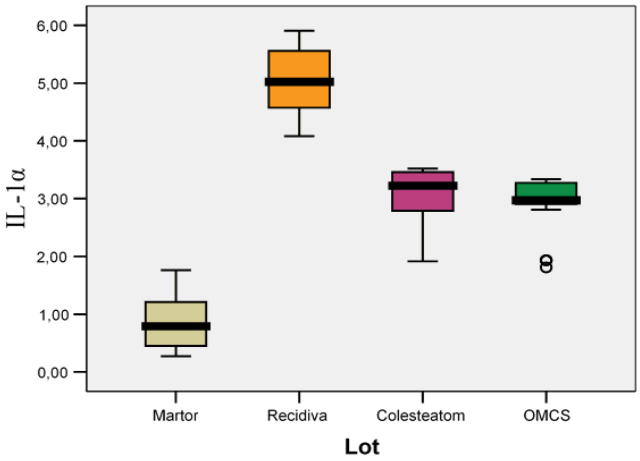

Fig.35. *Mean IL-1α values compared to study groups*

IL-6 recorded the highest mean level in patients with CSOM, with variations from 57.23 pg / ml to 193.33 pg/ml, followed by that recorded in patients with cholesteatoma with variations between 240.62 pg / ml -519.63 pg / ml, significantly higher compared to the control group (316.59 pg / ml; 121.23 pg/ml (p = 0.001) *vs* 5.81 pg / ml; p = 0.001). The mean level recorded in patients with cholesteatoma recidivism was slightly lower compared to that recorded in patients with cholesteastoma, but significantly higher compared to the control group (117.77 pg / ml; 121.23 pg / ml (p = 0.51) *vs* 5.81 pg / ml; p = 0.001) (Fig. 41).

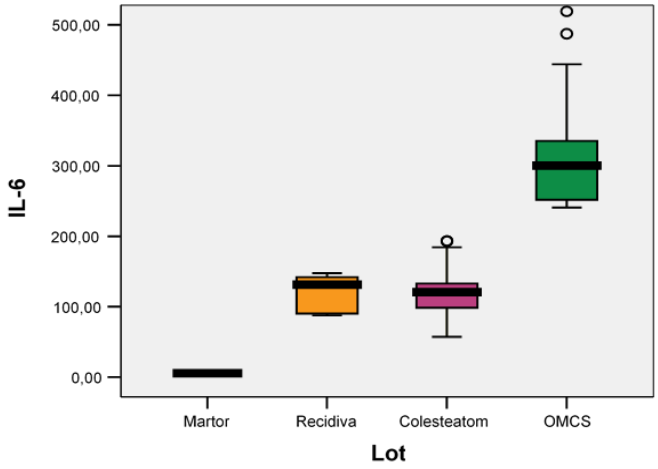

Fig.41. *Mean values of IL-6 (pg / ml) compared to study groups*

Analyzing the values obtained from IL-8 dosage, it can be observed that, in the CSOM group, IL-8 varied from 27.95 pg / ml to 83.58 pg / ml, and in patients with cholesteatoma the variation was within the range 31.72 pg / ml - 77.39 pg / ml, registering the lowest average level in the patients from control group, significantly lower compared to the levels recorded in the patients with cholesteastoma and CSOM (53.91 pg / ml; 54, 20 pg / ml *vs* 34.31 pg / ml; p = 0.001).

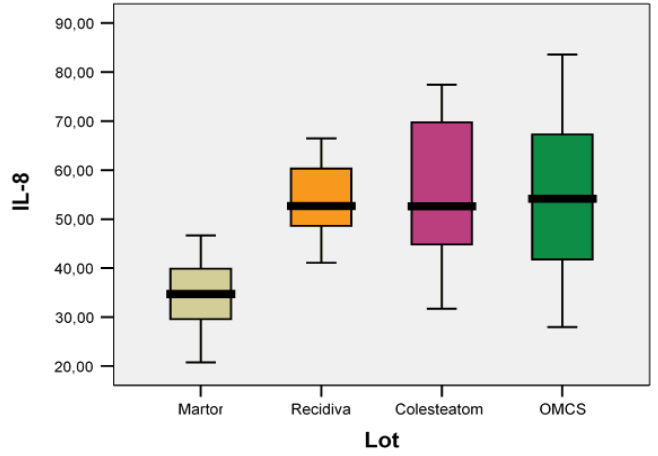

Fig.47. *Mean values of IL-8 (pg / ml) compared to study groups*

The mean level recorded in patients with cholesteatoma recidivism was slightly lower compared to that recorded in patients with cholesteatoma or CSOM (53.91 pg / ml; 54.20 pg / ml *vs* 53.74 pg / ml; p = 0.944), but significantly higher compared to the control group (34.31 pg / ml *vs* 53.74 pg / ml; p = 0.001) (Fig. 47).

3.4. Discutions

In the study made by Sagiroglu et al. in children, the values of CAT activity range from 0.48 to 28.23 in patients with chronic serous otitis media, between 0.14 and 11.41 in patients with acute otitis media and between 0.35 and 15.28 in the control group. The highest values were thus recorded in chronic pathologies, the group of healthy children having the minimum values (Sagiroglu et al., 2019). The results obtained were thus similar to those obtained in the present study.

Similar results to the present study regarding SOD values were obtained in the study conducted in Turkey, in which the average in patients with cholesteatoma was 20.07 and in the control group of healthy individuals it was 34.46. The same study specifies that there were no statistically significant differences between the SOD values measured from the serum and from the tissue taken intraoperatively, arguing that the serum dosage of the oxidative stress markers is sufficient for the assessment of oxidant status (Garca et al., 2015).

Sagiroglu et al. studies the oxidative status in children and finds SOD values that vary in wider intervals, respectively 15.56-783.02 in patients with chronic serous otitis media, 18.57-931.35 in patients with acute otitis media and 31.21- 657.57 in the control group, with no clear effect of the enzyme in acute and chronic pathology (Sagiroglu et al., 2019). In an experiment conducted on guinea pigs, elevated levels of SOD have been shown in the blood of patients with acute serous otitis media, compared with those without otitis (Aktan et al., 2003).

Garca et al. in 2015 find similar values of CAT from tissue and serum in patients with CSOM with and without cholesteatoma, and lower levels compared to the control group of healthy patients (Garca et al., 2015).

In an experiment performed on guinea pigs with serous otitis media induced by histamine injection, the CAT values were not statistically different from those in the control group (Aktan et al., 2003).

The CAT values obtained in a study performed on children were lower in those with adenoids hypertrophy and chronic serous otitis media and of those with only adenoids hypertrophy compared to the control group of healthy children (Yariktas et al, 2004). Similar results were obtained by Yilmaz et al.

which studied preoperative oxidant and antioxidant levels and one month postoperatively in children with adenoids hypertrophy and chronic bilateral serous otitis media (Yilmaz et al, 2004).

Similar results with high serum MDA values in the control group compared with the study group were also obtained by Garca et al. in a study where the mean value of MDA in patients was 4.85 ± 1.58 nmol / μL, and in the control group 1.72 ± 0.4 nmol / μL. Comparing the study groups, in those with CSOM without cholesteatoma the value was 4.85 ± 1.21 nmol / μL and in those with CSOM with cholesteatoma the value was 5.35 ± 2.06 nmol/μL (Garca et al., 2013). Similar results were obtained by Callejo et al. who evaluated the level of lipid peroxidation in patients with cholesteatoma, CSOM without cholesteatoma and acute otitis media (Callejo et al., 2000).

In all patient groups the serum levels of TAC were statistically significantly lower compared to the group of healthy people. In 2013, Garca et al. also observed a decrease TAC values in serum, identifying values of 97.0 ± 13.7 mmolEq / l in the patient group and 433 ± 130 mmolEq / l in healthy individuals. Comparing groups of patients with CSOM in those without cholesteatoma TAC was 96.0 ± 12.5 mmolEq / l, and in those with cholesteatoma 98.8 ± 15.9 mmolEq / l (Garca et al., 2013), non-existent statistical differences (Garca et al., 2013).

In the present study, analyzing the values obtained for IL-1α, it can be observed that in the patients with cholesteatoma and CSOM there were significantly lower values compared to those with cholesteatoma recidivism. Barzilai et al. measured the concentration of IL-1 in the middle ear fluid and showed that IL-1 levels were significantly higher in cases with acute otitis media with a positive bacterial culture than in cases with a negative bacterial culture. IL-1 levels decreased on days 4-5 of antibiotic therapy unrelated to bacterial eradication (Barzilai et al., 1999).

IL-6 appears to play an important role in inflammation in the otitis media pathology. Increased values of IL-1, IL-6 and TNF-α were correlated with serous otitis media in children (Yellon et al., 1995). Similar results with increased serum levels of IL-6 were obtained in a recent study showing that IL-6, metalloproteinase-2 and metalloproteinase-9 are related to the degree of destruction in the middle ear and the severity of the disease. (Wu et al., 2019).

Increased levels of IL-8, such as those obtained in the present study, were also identified in middle ear fluid in serous otitis media, with higher values in children than in adults (Hotomi et al., 1999). In guinea pigs experiments, TNF-α and IL-1β peaked before IL-8, suggesting that it is produced by inflammatory

cells accumulated by the influence of TNF-α and IL-1β (Sato et al., 1999; Juhn et al., 2008).

3.5. Conclusions

1. Oxidative stress, which is associated with a decrease in antioxidant levels, is involved in the pathogenesis of CSOM with and without cholesteatoma.

2. The present study identifies statistically low levels of SOD, TAC and increased levels of CAT and MDA in all study groups (especially in patients with cholesteatoma) compared to the control group, composed of healthy individuals, which confirms intensity of oxidative stress in disease conditions.

3. Of the inflammatory markers analyzed, IL-1α and IL-6 recorded statistically significantly higher values (the highest in patients with CSOM) compared to the control group. The direct correlation between the serum value of IL-6 and TAC in the group of patients with cholesteatoma demonstrates the direct relationship between oxidative stress and the inflammatory process in this pathology.

4. Although serum IL-8 levels were statistically significantly higher compared to the control, correlations between IL-8 and oxidative stress markers varied depending on the pathology.

5. We can say that inflammatory mediators play a central role in the pathogenesis of CSOM and cholesteatoma maintaining a systemic and local inflammatory response. This could be one of the reasons for the progression of the ear condition and the cholesteatoma recidivism. Further studies are needed to develop a possible alternative therapy that could be applied before, in or after surgical intervention.

4. Study 2: evaluation of the quality of life of patients with chronic suppurative otitis media using COMQ-12 questionnaire

3.6. Introduction

CSOM associates symptoms such as otorrhea, local pain, hearing loss, who that can lead to communication problems, impeding social interaction and having a negative impact on professional life (Ralli et al., 2017).

3.7. Material and method

The Romanian version of the COMQ-12 questionnaire was obtained by translating the original questionnaire from English into Romanian, with the prior consent of the authors, by three translators: a psychologist, an ENT

specialist and a bilingual translator. Subsequently, a reverse translation was made to ensure accuracy. The differences between the three translations were discussed and subsequently resolved by the translators. The psychologist had the role of adapting the contents of the questionnaire questions to the ideas, customs and social behavior of our society.

The COMQ-12 questionnaire was applied to a control group of 40 volunteers. For validation, the questionnaire was applied to a group consisting of 40 patients diagnosed with CSOM with and without cholesteatoma, admitted to the ENT Clinic of the Clinical Rehabilitation Hospital in Iasi. The questionnaire was applied before surgery and 6 months after surgical intervention.

4.3. Results

Compared by gender (19.16 vs 17.22; p = 0.395), age (18.10 vs 18.32; p = 0.919) or place of origin (18.24 vs 18.16; p = 0.970), the average score for symptoms did not show statistically significant differences (Table XVIII).

Severe impairment is more frequent in men (53.3%; p = 0.439), under 40 years of age (54.5%; p = 0.950) and in urban area patients (54.5%).

Compared by gender (11.95 *vs* 12.86; p = 0.328), age groups (12.42 *vs* 12.43; p = 0.994) or place of origin (11.86 *vs* 13.05), the average score for the impact on the lifestyle did not show statistically significant differences.

Severe impairment was most frequently observed in women (64.2%; p = 0.182), under 40 years of age (58.8%; p = 0.490) and in patients from rural areas (52.9%; p = 0.553).

By drawing the ROC curve it was found that gender, age and studies are not good predictors in the determinism of the demoralization caused by the ear problems, but the background has a 60% probability of determining this manifestation (AUC-0.600; IC 95: 0.417-0.783).

The risk scores generated by symptoms (p = 0.026) or impact on lifestyle were significantly correlated with the demoralization status caused by the ear problems. Patients who scored high on question 12 regarding overall impact had the highest risk score for symptoms or lifestyle impact.

In patients with CSOM, cut-off values of risk score according to specificity and sensitivity, for symptoms (AUC = 0.872; IC95: 0.724-1.050), with a sensitivity of 91.7% and a specificity of 87.2% was 10, and for impact (AUC = 0.671; IC95: 0.508-0.835), with a sensitivity of 75% and a specificity of 59% was 12.50.

The overall COMQ-12 score proves to be a good predictor in CSOM determinism (AUC = 0.853; 95% CI: 0.718-0.988).

Tabel XVIII. *Descriptive statistical indicators of the risk score for symptoms*

Caracteristics	N	Media	Std. Deviation	Std. Error	Confidence interval		Min	Max	p FANOVA test
					- 95% CI	+ 95% CI			
Total	40	18,20	6,68	1,06	16,06	20,34	4	28	
Gender									
Male	19	19,16	7,33	1,68	15,63	22,69	4	28	**0,395**
Female	21	17,33	6,09	1,33	14,56	20,10	7	26	
Age groups									
< 40 years	21	18,10	7,17	1,56	14,83	21,36	4	28	**0,919**
≥ 40 years	19	18,32	6,29	1,44	15,28	21,35	7	27	
Place of origin									
Urban	21	18,24	6,62	1,45	15,22	21,25	7	28	**0,970**
Rural	19	18,16	6,92	1,59	14,82	21,49	4	28	
Studies									
Primary education	3	11,33	3,21	1,86	3,35	19,32	9	15	**0,050**
Secondary education	10	16,67	5,78	1,83	17,76	26,04	11	28	
High school	18	19,44	6,06	1,43	13,65	19,68	7	27	
University education	9	21,90	7,58	2,53	13,61	25,27	4	28	

4.4. Discutions

The present study validates the COMQ-12 questionnaire in Romanian and evaluates the quality of life in patients with CSOM over 18 years, according to the initial study made by Phillips in 2014 (Philips et al, 2014), being the first questionnaire in Romania that evaluate this aspect.

Calculating the Cronbach's Alpha coefficient, we obtained a value of 0.788, a coefficient considered satisfactory to a value greater than 0.7, which shows a good internal consistency of the questionnaire (Tavakol and Dennick,

2011). For the questionnaire initially developed by Phillips, the internal consistency was 0.889 (Philips et al., 2014).

Overall, 47.5% of the respondents had a moderate quality of life and 30% a severe one. Analyzing the occurrence of local symptoms by gender, age group and socioeconomic status, the value of the mean symptom score did not show statistically significant differences, which suggests that the local symptomatology is perceived by patients in a similar way. Thus one of the four dimensions of quality of life related to health is evaluated, namely, the physical health that includes somatic perception and the impact of the symptoms of the disease.

The impact on daily activities has a high level, 50% of those interviewed declaring the disturbance of the daily worries at least once a month. A percentage of 2.5% of the studied group has an almost daily impairment of daily activities and 22.5% at least once a week. Thus, the ear disease presents a factor that negatively influences the quality of life of the individual. Preventing the daily routine leads to a decrease in self-care capacity.

By centralizing the data obtained by applying this questionnaire, we can say that the demographic aspects do not statistically significantly affect the deterioration of the well-being caused by the ear condition. The place of origin is involved in the determinism of the demoralization caused by 60% of the ear disorder. This is associated with economic resources, educational level and access to health services. There are studies that demonstrate the association between socio-economic status and physical and mental health. The risk scores generated by some symptoms or by a certain lifestyle increase with the deterioration of the mental state (Alvarez-Galvez et al, 2013).

4.5. Conclusions

The Romanian version of the COMQ-12 questionnaire is the first valid tool that evaluate the quality of life in patients with CSOM.

2. This questionnaire is built to obtain information about the most important symptoms for the patient and how they influence them, allowing the clinician to choose an appropriate management strategy in accordance with the patient's expectations and needs.

3. Analyzing the values obtained from its application, it can be observed a negative impact of the ear condition, regardless of its type on the different life aspects, which are improved with surgery.

4. No major difficulties in translating or applying the questionnaire were identified. Sometimes the assistance of the medical staff was necessary to

answer the questionnaire, the patients sometimes having difficulties in understanding the questions.

5. Study 3: evaluation of the quality of life of patients with chronic suppurative otitis media using COMOT-15 questionnaire

5.1. Introduction

The COMOT-15 questionnaire was developed in 2009 by Baumann and assesses the quality of life of patients with CSOM (Baumann et al, 2009). Until now it has been translated and validated in the Kannada and Nepalese languages (Phrabu et al, 2018; Shrestha et al, 2017), being used for comparing the effects of different surgical techniques (Shrestha et al, 2017; Baumann et al, 2011). In contrast to COMQ-12, COMOT-15 assesses in detail the impact of hearing loss on the quality of life of the patient with CSOM with and without cholesteatoma.

5.2. Material and method

The Romanian version of the COMOT-15 questionnaire was obtained by translating, with the author's consent, the original questionnaire from German into Romanian by three different translators: a psychologist, an ENT specialist and a bilingual translator, followed by a backword translation, to ensure accuracy. The differences between the translations were discussed and resolved by the translators. The psychologist has adapted the content of the questions to the ideas, customs and social behavior of our society.

The COMOT-15 questionnaire was applied to a control group of 50 volunteers. For validation, the questionnaire was applied to a group consisting of a total of 50 patients diagnosed with CSOM with and without cholesteatoma, admitted to the ENT Clinic of the Clinical Rehabilitation Hospital from Iasi. The questionnaire was applied in a first stage before surgery and later at a 6 month after surgery.

The results were centralized in an SPSS database version 18.0 and processed with the specific statistical functions, at a significance threshold of 95%.

5.3. Results

Depending on the epidemiological characteristics, the type of disease has the following particularities:

- cholesteatoma was more frequent in women (61.8%) and CSOM in men (56.3%), but the differences were not statistically significant ($p = 0.232$);

- cholesteatoma was slightly more frequent in the age group over 40 years (52.9%), and CSOM was found in both age groups (50%) (p = 0.846);

- CSOM was more frequent in patients from urban areas (62.5%), while cholesteatoma was found in both cases (50%) (p = 0.406).

Before surgery all patients performed a tone audiogram. The aerian conduction in patients with COM with cholesteatoma measured on the frequency of 0.5 KHz ranged from 25 dB to 120 dB, recording an average level of 54.20 ± 20.21 dB. On the frequency of 1 KHz the average value was 56.90 dB, at 2 KHz the average was 52.80 dB and at 4 KHz the value was the highest of 62 KHz. The mean values close to the median values and the result of the Skewness test <2, regardless of the frequency at which the determinations were made, suggest that the series of bone conduction values in patients with cholesteatoma were homogeneous. The mean level of bone conduction increased significantly with increasing frequency from 0.5 KHz to 4 KHz (18.20 *vs* 26.60; p = 0.001). Subsequently the difference between air and bone management (AB gap) was calculated. The AB gap calculated at a frequency of 0.5 KHz varied widely (36.74%) from 10 to 60, recording an average level of 36.0 ± 11.69 KHz.

The application of Reability Statistics on the case of the control group, for the validation of the questions in the questionnaire revealed a Cronbach's Alpha coefficient = 0.972, so the questionnaire applied has a good consistency.

For items 1-15, a score was calculated, which can range from 0 (good) to 75 (bad). In the case study, the total score in patients with cholesteatoma ranged from 21 to 62, with an average level of 44.88 ± 11.03, which shows that the ear conditions moderately affect the well-being, compared to the CSOM group (44.88 *vs* 44.69; Bonferroni post-hoc p = 0.999). Both mean scores were significantly higher compared to the mean level recorded in the control group (44.88; 44.69 *vs* 3.86; p = 0.001).

Compared by gender (46.09 *vs* 42.61; p = 0.289), age groups (45.96 *vs* 42.46; p = 0.284) or place of origin (44.70 *vs* 43.48; p = 0.710), the average score for problems due to the hearing did not register statistically significant differences. Related to the educational level, there were significant differences in the average risk score, the lowest value being registered in patients with primary education, and the highest average value in those with secondary education.

Severe impairment is most commonly seen in women (54.2%; p = 0.836), under 40 years of age (54.2%; p = 0.740) and urban patients (54.2%).

The multivariate analysis showed that the risk was determined by the older age in conjunction with lower values of air and bone conduction determined at 0.5 and 2 KHz.

5.4. Discutions

The COMOT-15 questionnaire, which was the basis for the development of COMQ-12 questionnaire, wide spread, being translated and validated in several languages, evaluates the impact of the hearing loss on the patient with CSOM, making a subjective evaluation of the local and general symptoms.

The local symptoms affect the social life, leading to a predisposition of integration deficit, isolation followed by a decrease of the self-confidence. The COMOT-15 questionnaire focus on the severity of local symptoms determined by the CSOM. Lucidi et al. uses this specific questionnaire to evaluate the quality of life at 12 months after surgery, in patients with cholesteatoma, in case of using different surgical techniques, closed technique *vs* open technique due to the detailed analysis of local symptoms and the easy way to apply them (Lucidi et al., 2019).

Calculating the total score for all questions in the questionnaire were obtained for patients with cholesteatoma values from 21 to 62 points (out of the maximum possible 75), with an average of 44.88 ± 11.03, which highlights that, the ear condition moderately affect the well-being, aspect compared with the CSOM group, where an average of 44.69 ± 12.58 was obtained. Both mean scores were significantly higher compared to the average level recorded in the control group, which had a mean value of 3.86 ± 6.9. Phrabu obtained in a study an average value of 23.8 ± 6.17 (Phrabu et al., 2018), while in the study conducted by Baumann, the average value was 46.4 ± 18.8 (Baumann et al., 2011), similar to the present study.

Postoperatively, at 6 months, the total mean score was 27.2 ± 10.2, of which the local ear symptoms had a mean value of 6.5 ± 4.7, the hearing function 7.4 ± 3.7, mental health 8.6 ± 3.9. The mean value obtained was similar to that obtained by Baumann, respectively 38.4 ± 20.5. However, the subscale scores had lower values of 27.7 ± 18.0, 56.0 ± 30.4 and 40.1 ± 28.6 (Baumann et al., 2011).

5.5. Conclusions

1. The Romanian version of the COMOT-15 questionnaire is a valid tool with which a quality of life assessment can be performed in patients with CSOM, focusing on the auditory function. The questionnaire can be used to monitor the post-operative evolution in different surgical techniques, such as

closed / open technique, tympanoplasty. The correlation of the results obtained with the objective evaluation by audiometry leads to a better monitoring of the patients and to an improvement of the medical record.

2. The Romanian language version of the questionnaire has a good internal consistency, which can be used as a tool for measuring the quality of life.

3. About 50% of patients with CSOM with cholesteatoma have a severe risk score, with a low quality of life.

4. The demographic characteristics do not significantly influence the deterioration of the well-being caused by the ear conditions.

7. Original elements

In order to establish the role of oxidative stress and proinflammatory markers in the pathophysiology of cholesteatoma, the values obtained in the group of patients with CSOM with cholesteatoma, the object of the present study, were analyzed in comparison with CSOM without cholesteatoma, with recurrence of cholesteatoma and with a lot of healty people. The establishment of correlations between the type of ear pathology, the level of proinflammatory cytokines and the production of reactive oxygen species and the antioxidant system has not been realized so far. An excessive response of the body to aggression of the factors could cause the progression of the disease, but also a sustained inflammatory response that inhibits the recovery of healthy tissue, causing pathological changes.

This study is the first in Romania who evaluate the quality of life in patients with CSOM. There is an evaluation of the impact of the disease on the daily activities, the social integration, the degree of addressability to the medical services as well as the general impact on the quality of life.

8. Future prospects

The evidence of involvement in the pathophysiology of otitis media with cholesteatoma and the cholesteatoma recidivism of oxidative stress and cytokines IL-1α, IL-6, IL-10 allows the development of complementary therapies in CSOM with and without cholesteatoma and treatments that could prevent / slow recidivism rate. This could be achieved by administering local and / or general antioxidant molecules. The identification of serum levels of CAT and preoperative MDA could determine the degree of ear condition. For

this, studies are needed in which the serum variation of antioxidant and oxidizing enzymes can be monitored at different times. It is also possible to investigate the involvement of vitamins (vitamin A, vitamin C and vitamin E) whose efficacy has been proven both in reducing oxidative stress and in reducing the rate of progression or progression of CSOM with and without cholesteatoma.

The development of quality of life assessment tools in patients with CSOM with and without cholesteatoma allows the personalization of the treatment protocols and allows the analysis of the emotional, social and physical impact of this pathology on the individual.

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