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MODERN VIEW ON THE DIAGNOSIS AND TREATMENT OF TYMPANOSCLEROSIS

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(Monograph)

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Монография является результатом научного исследования, основные результаты которого изложены в научных исследованиях авторов. В монографии, авторами систематизированы результаты собственных исследований и представлены данные публикаций мировой литературы о этиопатогенезе, диагностики, лечения, прогнозирования и профилактики тимпаносклероза.

Монография предназначена для повышения уровня знаний и квалификации магистров, клинических ординаторов, студентов, стажеров исследователей, научных сотрудников, врачей оториноларингологов и поможет в решении следующих задач:

-повысить уровень знаний о ТСК;

-обосновать методы диагностики ТСК;

-разработать методы поэтапного лечения ТСК.

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LIST OF ABBREVIATIONS

AC, VP – Air conduction
ABG, VKZ – Air-bone gap
CD – Cluster of differentiation
CTL – Cytotoxic lymphocyte
HLA – Human leukocyte antigen
IFN, IFN - Interferon
IL – Interleukin
IL-1β – Interleukin-1 beta
MHC – Major Histocompatibility Complex
TCR – T cell receptor
TH – T-helper
TNF – Tumor necrosis factor
RTL – Regulatory T lymphocyte
AG – Antigen
WHO – World Health Organization
NK – Natural killer
BC – Bone Conduction
CT – Computer tomography
MSCT – Multi-slice computer tomography
EAC – External auditory canal
PB – Peripheral blood
COP – Complete ossicle prosthesis
TSC – Tympanic sclerosis
UT – Ultrasonic therapy
CPOM- Chronic purulent otitis media
CAO– Chain of auditory ossicles

PREFACE

All over the world the hearing loss is one of the six main factors affecting quality of life. According to WHO, "... nowadays, chronic purulent otitis media (CPOM) occurs in 2-6% of the world's population, 60% of whom suffer from significant and persistent hearing loss. Severe hearing loss means permanent disability and is a problem of social and economic significance (E.V. Garov et al., 2013). Tympanic sclerosis is often found in the structure of ENT diseases in adults and children (J. Jeong., 2022; Sh.E. Amonov et al., 2022)

Tympanic sclerosis is the chronic non-purulent disease of the middle ear, the distinctive characteristic of which is the formation of specific sclerotic foci in the thickness of the mucous membrane of the middle ear or eardrum, which leads to damage of sound-conducting apparatus and hearing loss.

Globally, tympanic sclerosis (TSC) is detected in 3.3-38% of patients suffering from chronic purulent otitis media (CPOM). (Nemati Shadman et al.,2021). The authors show that with perforation of tympanic membrane TS occurs in 65-94%, and in its absence - in 5.3-35% (No K-U et al., 2010). In the presence of bilateral CPOM, manifestations of TS in 48.1-95% of cases are binaural in nature, but the severity of its clinical and morphological manifestations are often asymmetrical, and the size of the perforation does not reflect the volume of TSC- foci (Chernushevich I.I., 2011, Sinem Gökçe., 2019). The lack of consensus on some aspects of the pathogenesis of this disease determines the relevance of the problem. It is advisable to study the cause, optimize diagnosis and surgical treatment of patients with tympanic sclerosis.

Despite early diagnosis and reduction of somatic diseases complications, among various segments of population in our country many good results were taken, but there were some significant problems in the healthcare system. Among them, the identification and prevention of chronic hearing diseases were very important.

In the action strategy for the five priority areas of development of the Republic of Uzbekistan for 2017-2021, special attention is paid to

“...strengthening family health, protecting motherhood and childhood, expanding access to quality medical services for mothers and children, providing them with specialized and high-tech medical care, as well as the implementation of priority tasks to implement comprehensive measures to reduce infant and child mortality.”

In this regard, it is advisable to carry out such research as raising the quality of medical care for patients to a new level, developing and improving modern high-tech methods for identifying, diagnosing and treating patients with chronic purulent otitis media CPOM (Chronic purulent otitis media) with tympanic sclerosis.

CHAPTER I. THE MODERN VIEWS ON CLINICAL AND DIAGNOSTIC ASPECTS AND TREATMENT OF TYMPANIC SCLEROSIS (LITERATURE REVIEW)

§ 1.Epidemiology of tympanic sclerosis

Tympanic sclerosis is considered a pathological condition of middle ear, characterized by pathological changes such as hyaline degeneration and calcification or ossification of the tympanic membrane, the mucous membrane of the tympanic cavity and the connective tissue of the submucosa. If these calcified plaques form in the osseous chain, they can lead to conductive mixed hearing loss. At the same time, TSC most often leads to severe hearing loss, permanent disability and, therefore, has not only social, but also economic significance (Chernushevich I.I. et al., 2013, Nemati, Shadman, etal., 2021.) .

Among patients with chronic inflammatory pathologies of the hearing organ, patients with tympanic sclerosis account for 43%-47.8% ,(Chernushevich I.I., Agazaryan A.G., Anikin I.A., et al .,2018; Sinem Gökçe et al.;2013).

One of the etiological factors in the development of tympanic sclerosis is inflammation, and the mechanism of formation of tympanic sclerotic changes is ectopic calcification. (Shahzad F.2015; P. Flint.,2015 Nemati, Shadman, et al.,2021).

In 33% of patients with chronic purulent otitis media, Pau H. W., Just T. (2010) the identified changes characteristic of TSC were revealed, while according to A. Pirodda et al. (2012) this index was 30%, according to V.V. Gar - 31%, S.V. Ryazantseva et al. (2005) – 19.8%, Sinem Gökçe et al. (2011-2013) – 47.8%, Nitesh Mohans et al. (2014) – 65%, and according to Dong Z (2022) – 24.5% .

In recent years some otorhinolaryngologists have noted the tendency towards increase in the prevalence of tympanic sclerosis (Agazaryan A.G. et al. 2018; Nemati, Shadman, et al., 2021).

Among the possible reasons for this increase can be the irrational antibiotic therapy at treatment of chronic hepatitis A, leading to the dissemination of antibiotic-resistant strains of microorganisms. As a

result, the clinical course of CHSO changes - exacerbations of the disease become longer lasting and resistant to taken therapy with the outcome of tympanic sclerosis formation .

According to most authors, the formation of tympanic sclerosis begins in childhood or adolescence, and the trigger point is the inflammatory process in the middle ear . The experimental and clinical studies have confirmed that tympanic sclerosis was the possible outcome of various otitis media (P. P. Flint et al. P. F. et al. 2015) - both chronic and acute catarrhal, purulent and including exudative otitis . It is also known that the development of tympanic sclerosis can be the consequence of traumatic or everyday damage of the eardrum, including the use of a tympanic ventilation tube at treatment of exudative otitis media. The reported incidence of TSC after shunt placement ranges from 28.3% to 61.0% .

The pathogenesis of this disease continues to be studied, despite the comparative clarity of tympanic sclerosis etiology. Despite many studies having been conducted to present day, no one could explain the fact that in some patients, after the single short-term suppuration from the ear, the disease progressed very quickly, while in other patients, despite frequent and prolonged exacerbations of chronic otitis, there were no tympanic-sclerotic manifestations.

§ 1.2. On the issue of sclerotic changes pathophysiology in the middle ear cavity

There are many factors are involved in disease pathogenesis which are witnessed by the results having carried out in different years.

In some researches the attention is payed to the immunological aspects of tympanic sclerosis . The analyses of swabs from the mucous membrane of the middle ear in patients with tympanic sclerosis showed the increase of interleukin-8 content, which have both pro-inflammatory property, and also, regulate cellular calcium metabolism (Miniakhmetova R. R., 2010), and, at the same time, the concentration of interleukin-6, according to Pawelczyk, Tadeusz et al. (2014), on the contrary, is reduced .

The genetic predisposition to tympanic sclerosis is supported by the probable association of tympanic sclerosis with HLA antigens –B35 and DR3 (Chernushevich I. I., Anikin I. A., Miniakhmetova R. R.;2008).

Some scientists in their studies found that TSC often occurs in females, for example, Nitesh Mohan (2014) in his own studies proved that 60% of patients were female .

The presence of local metabolic disorders in pathogenesis of TSC was also studied, for example, the role of free radicals was researched by S. Atmaca et al (2008). There were taken investigations at the result of those it was determined the activity increase of inducible nitric oxide synthetase (iNOS), an enzyme that is produced by macrophages in response to inflammation and induces the production of nitric oxide (NO), the function of that is oxidation in normal antibacterial defense reactions, as well as in pathological autoimmune reactions**.** The correlation link between decrease of cellular antioxidants in content, such as superoxide dismutase and catalase, and, the development of tympanic sclerosis (T. Karlidag.2004; Nemati, Shadman, etal.2021) .

N. Koktein et al. (2016) in experiment on guinea pigs proved that local and oral use of Negella oil pigs have proven that topical and oral use of Negella Sativa oil with antioxidant, anti-inflammatory and bactericidal properties prevents the development of myringo-sclerosis after myringotomy.

The role of calcium metabolism disorders in patients with tympanic sclerosis was determined; the use of calcium channel blockers gave true positive results in the prevention of TSC .

The role of one from the main non-collagenous proteins of bone tissue, osteopontin was revealed, which participated in regulation of bone resorption and pathological calcification. This conclusion was made at the result of immuno-histochemical analysis of biopsies from foci of tympanic sclerosis, where the protein osteopontin was determined .

The high lysosomal activity of connective tissue cells was revealed, which can lead to changes in the structure of collagen fibers and calcification. The data on significant increase the levels of parathyroid hormone and the

bone resorption marker β-CrossLaps in the blood of patients with tympanic sclerosis were shown, with simultaneous decrease concentration of vitamin D, which regulates osteogenesis. It witnessed on imbalance in calcium metabolism system, contributing to ectopic calcification in the mucous membrane of middle ear (R. R. Miniakhmetova, 2010;).

The experimental studies showed the significant contribution to the degradation of extracellular matrix structures of matrix metallo-proteinases of the family of Zn- and Ca-bound endopeptidases, which caused the development of sclerotic changes (H. Aslan et al. 2011; Nemati, Shadman, et al. 2021) .

It was determined that in patients with atherosclerotic transformations and Peroni's disease, TSC occurred more often than in patients without the above diseases, which witnessed on common mechanisms of those diseases.

Despite the fact that the presence of protein disorders and mineral metabolism of connective tissue in patients with tympanic sclerosis was proven both in clinical and experimental studies, the issues of morphological formation of sclerotic plaques have not been fully studied. The influence issues of dysfunction of autonomic nervous system, in particular, the hypothalamic-pituitary system on formation of sclerotic processes were studied. The hypotheses on aggravation of morphological destruction under the influence of inflammatory process, was put forward, which were supported by prolonged psycho-emotional stress, concomitant somatic diseases, and irrational use of pharmacological drugs, which in its turn, caused immunological shifts .

§1.3. Morphological changes in the anatomical structures of the middle ear with tympanic sclerosis

Morphological changes in tympanic sclerosis were presented limited from surrounding tissues by white lens-shaped formations, which were often localized in the cavity of middle ear and/or on the eardrum and in its thickness. M. Mansour et al. (2018) described tympanic sclerosis as hyaline degeneration of connective tissue with deposition of calcareous salts and formation of new bone .

The otoscopy determined the superficial localization of tympanic sclerosis formations, which are located exceptionally in the connective tissue layer tympanic cavity wall or membrane .

Depending on patho-morphological changes the plaques can be divided into: dystrophic, sclerotic, hyaline, petrified and mixed types .

The results of histological changes made it possible to distinguish early, intermediate and late forms of TSC. Early TSC in the histological picture was represented only by a violation of normal arrangement for connective tissue fibers. At intermediate TSC form the areas of hyalinization are determined; in the late form of TSC the characteristic foci of tympanic sclerosis with signs of calcification and/or ossification are histologically identified. The definition of "histological tympanic sclerosis" included focal manifestations of tympanic sclerosis on the stage of fibrinous swelling and hyalinosis, not detectable by oto-microscopy, which are characteristic for initial and preclinical forms of TSC .

The staged nature of sclerotic changes in TSC were proven. Stage 1 is reversible and it is characterized by damage to collagen fibers. Stage 2 is characterized by excessive collagen formation, which is caused by fibroblastic invasion. Subsequently, the collagen fibers become thinner and melt, hyalinize, resulting in the formation of a homogeneous mass with indistinguishable fibers, which in a macro-preparation appears as soft white cartilaginous tissue or as compacted tissue with a rubber-like structure. Stage 3 of tympanic sclerosis is irreversible, characterized by calcification and ossification .

According to the authors, the tympanic sclerosis is the final stage of catarrhal otitis media. At the same time, the study of cytokines level and histological features of surgical material indicate the incompleteness of productive stage for inflammatory process .

Depending on nature of inflammation, the fibrous process proceeds according to type of epimorphosis, where the tissue defect is compensated by granulation tissue and became transformed into scar, and endo-morphosis, where the tissue defect is compensated by granulation tissue and transformed into a scar, and endo-morphosis, in which the fibrosis is observed in the mucous membrane itself. For tympanic sclerosis is it is

characterized by endo-morphosis, where the dense conglomerates are formed in tympanic cavity and membrane as the focal form. The layered structure of sclerotic plaques is caused by multiple cycles of calcification of hyaline formations and formation of plates [A. Selcuk et al. 2008; Bodachenko K.A. et al. 2011]. The ossification of tympanic sclerotic focus is a little-studied aspect of morphological changes at TSC. Some authors mark out the variant of tympanic sclerotic plaque "with signs of ossification." The ossification of plaque can be explained by increased osteogenic function of muco-periosteum and degeneration of bone formations in tympanic cavity, that is, the formation of bone sequesters. Macroscopically ossified plaque has bone density, and is easily separated from underlying bone tissue during its removal; it is usually localized in the medial wall of tympanic cavity .

The cause of destruction for bone structures in the middle ear in COM is often cholesteatoma and caries-granulation processes, less often – tympanic sclerosis . At cholesteatoma the destruction of bone tissue is caused by its passive growth and the activity of the peri-matrix, which leads to the destruction of not only the auditory ossicles, but also the temporal bone. While in tympanic sclerosis the bone destruction would be the consequence of dystrophic and necrotic processes due to pathological processes in muco-periosteum and disruption of the trophism of underlying bone tissue, and it has the limited character .

The sclerotic changes are distributed unevenly in the middle ear cavity. More often the sclerosis is determined in the area of muo-periosteum, less often – sub-epithelial sclerosis. Muco-periosteum is histologically similar to embryonic connective tissue and also has ability to form bone and cartilage tissue in response to the inflammatory process. Thus, the process of bone formation structure is due to the synthesis of connective tissue from precursor cells transformed into osteoblasts [28,43]. The morphological substrate of TSC relapse is manifested by new bone formation among soft tissue structures, followed by degeneration similar type of avascular necrotic process (R.R. Miniakhmetova 2010).

It was determined that at the beginning of pathological process, the granulation tissue is formed on the mucous membrane, followed by its

replacement with scar tissue; later, the scar tissue transforms into hyaline tissue, then calcifies, and even ossifies. At the same time, TSC should not be considered as a direct result of purulent inflammation, and a tympanic sclerotic plaque as a derivative of granulation tissue (A. Selcuk et al. 2008; M.H. Bhaya et al. 2003; Bodachenko K.A. et al. 2011).

Unlike other inflammatory processes, at TSC there is no reaction to the plaque from the surrounding tissue - the characteristic inflammatory shaft and scar capsule are not detected, but in the plaque itself it can be seen the signs of chronic, sluggish inflammation with a predominance of sclerotic changes, which indicates that the process is ancient (A. Selcuk et al.2008; M. Ferri et al.2004; Tukaj C, Kuczkowski J,).

The histochemical analysis of tympanic sclerotic plaques, free of lime, determines the presence of glycosaminoglycans, at the same time, the ossified tissue does not react to glycosaminoglycans. These facts witness on formation of foci for tympanic sclerosis because of dystrophic changes mechanisms the main substance and fibers of connective tissue .

§ 1.4. The clinical and diagnostic characteristics of tympanic sclerosis

TSC is generally considered to be the independent nosological unit with characteristic etiopathogenetic and clinical-morphological features.

At TSC in patients with COM perforation of the tympanic membrane is determined, while SCT associated with adhesive or exudative otitis, the tympanic membrane would be apparently intact. Depending on the integrity of tympanic membrane, TSC was divided into “open” and “closed” .

Previously it was believed that the severity of disease was not depended on the integrity of eardrum (I.B. Soldatova and V.R. Goffman 2002), but the research having carried out by K. Y. Ho et al. (2010) , determined the relationship between the degree of eardrum damage and the level of destruction formations in middle ear at patients with TSC. At the result, the classification was proposed, according to which 3 clinical forms of this disease were identified. According to the author, depending on damage degree in eardrum, it was possible to predict the level of lesion

of auditory ossicles, and, thereby, to plan the volume of surgical intervention.

In case of TSC with concomitant chronic purulent otitis media, the long-term remission was observed; during exacerbations, mucous or mucopurulent discharge was noted .

Bilateral COM was usually accompanied by binaural tympanic sclerosis, but the clinical and morphological picture was often asymmetrical. The frequency and expressiveness of pathological process in one ear are directly correlated with
the severity and hazard process in the other (A. Larim et al.2021) .

The observed hearing loss at TSC was usually conductive, less often mixed and sensorineural and caused by the combination of several reasons. The main reasons are the presence of eardrum perforation, limitation of its mobility, defects of the auditory ossicles, and limitation of their mobility due to their fixation with TSC foci .

Hearing loss during TSC, according to A. Larm et al. (2021), is insignificant, but by the other authors the pronounced degree of hearing loss can be observed. It depends on the extent of process, the localization of plaques relative to the ossicular chain and its histological structure .

At localization TSC foci on the tympanic membrane, the bone-air interval is usually small. At widespread TSC, where the process is extended to the manubrium of malleus or the bone ring, the bone-air interval exceeds 40-45 dB (D.-C.C. Donditov, M.P. Ryabov; ; 2009) and is often accompanied by severe hearing loss and a subjective sensation of noise in the ear (Larem A. et al. ; 2021).

The typical location of TSC foci is the region of window, vestibule, the upper part of promontory and the zone of the facial nerve canal. According to the authors, this location of TSC foci was noted in 92.6% of cases, whiles the isolated damage of area occurred in 20.2%, and in combination with other areas (attic, promontorium, etc.) - in 72.4% of cases. According to observations of A. Larem (2021), TSC foci were identified in the thickness of the eardrum in 50.6%, and in the mucous membrane of middle ear was in 52.9% of cases.

The area of the tympanic opening and the window of the cochlea is a rare localization of tympatic sclerotic foci - 2-3% of cases. In 17.6% of cases, the lesions are located near the auditory ossicles and in 5.8% of cases in the mastoid process. According to Z. Kizilkaya (2008), the multi-focality of the process was determined in 44.1% of patients, similar data were obtained by K.Y.Ho (2010) - 51.2%.

In a study performed by K. Kaur et al. (2006) in 21.1% of cases, fixation was detected, and in 7.9% of cases, caries and destruction of ossicular chain were determined. In studies by K.B.Teufert and A.De La Cruz (2002), the fixation of malleus was shown in 34.5%, incus – in 35.4%, stapes – in 35.9% of patients with TSC, characteristic "plaques" are determined in the base area stirrups, while the legs and head of the stirrup often remain free. In tympanic sclerosis obliterans, tympani sclerotic plaques fill the entire tympanic cavity from the facial nerve canal to the promontory, while the stapes is completely blocked.

The results of a histological study of the surgical material showed that the cause of fixation of the head of the malleus in the attic is not only the tympani sclerotic process (S. Martin et al., 2006). H. Aslan et al. (2010), established a combination of TSC and garnulations in 24% of cases, S. Asiri et al. (1999) and Y. A. Bayazit (2004) indicate a rare combination of TSC and cholesteatoma. Tympanosclerotic lesions prevent ingrowth Tympanosclerotic lesions prevent the ingrowth of the epidermis into the underlying bone tissue, and thereby serve as a barrier against the destructive effects of cholesteatoma. From a surgical point of view, limited and widespread forms of TSC are distinguished (Hashimoto S. A., 2000; A. Larem. A., 2021). A limited form is considered to be in which 1-2 areas in the middle ear cavity are affected - localized foci in the thickness of the tympanic membrane, involving the handle of the malleus or most of the auditory chain in the attic, while the labyrinthine windows and promontory are intact. Or, with preserved mobility of the incus and malleus, the plaques block the stapes and are localized in the region of the vestibular window (Kaur K., Sonkhya N., Bapna A. S.;2006).

In the common form of TSC, the lesions occupy several areas - both the attic and the area of the medial wall of the tympanic cavity.

Diagnostic errors of TCT are very rare, and, as a rule, are observed with small perforations or when tympsnic-sclerotic plaques are located deep in the middle ear cavity.

There are no pathognomonic symptoms characteristic of TSC during X-ray examination. An informative imaging method in the diagnosis of SCT is computed tomography (CT) (A. Larem et al. 2021). On a CT scan of the temporal bones, tympanic sclerotic plaques appear as single or multiple foci of uneven intensity (in the form of spots), in in some cases, they resemble a mesh in the tympanic cavity or in the thickness of the eardrum (A. Pirodda et al.2010). In addition, with the help of CT, it is possible to differentiate petrified and ossified lesions by density, and determine the presence or absence of a connection between plaques and the auditory chain (A. Pirodda et al.2010).

§ 1.5. Issues of surgical treatment and rehabilitation of patients with tympanic sclerosis

Earlier, there was an opinion that surgical intervention at tympanic sclerosis was considered ineffective, and, if it was necessary to remobilize a fixed stapes, it was also risky due to the inevitable impact on the inner ear. But nowadays the surgery is considered the most effective treatment of SCT []. However, the success of surgical intervention depends on the severity of sclerotic process, the location of the focus, the absence of stapes destruction and its mobility, and the integrity of auditory ossicles (Tsuzuki et al. 2006 Teufert K. B. De La Cruz A. 2002; Sakalli, E., 2014) .

The surgical intervention of tympanic plasty in patients with TSC usually includes the sanitation of middle ear, if possible, partial or complete removal of TSC foci with restoration of mobility for intact elements, restoration of its continuity (ossiculoplasty and myringoplasty) .

In order to restore the continuity of auditory ossicles both implants and auto-grafting are used (Sh. V. Japaridze et al., 2005; Tos M., 2004; M. Sanna et al., 2003). For myringoplasty the single-layer auto- grafts

are used, such as fascia, vein, perichondrium, adipose tissue, and rarely double-layer transplants (Koç A., Üneri C.2005).

Surgical intervention was carried out both multi-stage and in one stage. In the first case the surgical intervention was carried out in 2-3 stages, with debridement, myringoplasty and ossiculoplasty were performed with intervals from 6 to 24 months, but the advantage of one method over the other may be debatable (Z. Kizilkaya et al., 2008; E. Sakalli et al. ., 2015).

The advantage of one-stage intervention is the reduction of negative impact on the state of receptor apparatus for inner ear, the risk of injury may increase with each intervention on structures of tympanic cavity.

On the based studies the scientists came to conclusion that the lesions localized in thickness of the eardrum should be removed differentially, depending on size of plaque, and plaques which limit the mobility of the malleus handle must be removed. Also, TSC foci located in the anterior superior quadrant of tympanic membrane should be removed, since foci of this particular localization invariably limit its mobility (Kütük, Sinem Gökçe et al.;2019).

Many surgeons prefer to remove lesions associated with the annulus fibrous or localized in the area of the bed being prepared for the tympanic membrane graft, due to poor vascularization of TSC- lesions, which ensures satisfactory engraftment of transplant and mobility for formed neo-tympanic membrane .

The repeated surgical intervention is required in cases of functional deterioration for previously performed tympanic plasty due to lateralization of the neo-tympanic membrane, its thickening and limitation of mobility, lack of contact with ossicular chain or the installed ossicular prosthesis (Stankovic M. D. 2009) . In this case, the situation can be corrected in two ways. In the first case
the neoplastic membrane is left in the same place where it formed, and the diastasis between it and the prosthesis is removed by using a longer prosthesis. In the second case, the neo-tympanic membrane is lowered by first separating it, and the meato-tympanic flap is displaced to the level of tympanic ring, contact is made with the handle of malleus or the proximal

part of prosthesis [Dedmon M.M., O'Connell B.P; 2020]. With pronounced lateral displacement, the neo-tympanic membrane is completely removed and myringoplasty is repeated (Brackmann D. E., Shelton C., Arriaga M. A. 2001; K. Gyo et al. 2003).

The surgical tactics in relation to intra-tympanic foci of tympanic sclerosis are also ambiguous.

When determining a decrease in the mobility of malleus or its complete absence, one should not achieve mobility by rocking it, acting on the handle, which results in possibility of re-fixation of hammer. The mobilization of stapes is achieved by maximum removing plaques as completely as possible, while it is important to exclude direct impact on its base, which avoids rocking. In this case, TSC foci are removed with microsurgical needles and hooks to the annular ligament .

Due to the poor blood supply to TSC foci, the bleeding is usually not observed during surgery to remove plaques. And the plaques themselves are easily separated from the underlying tissues in layers, preserving the shape of the adjacent bone structures (H. Aslan et al. 2010).

The particular care is required when removing lesions localized in the area of the cochlear window, since damage to the membrane leads to deafness (M. M. Dedmon et al. 2020) .

After restoration of stapes mobility, and, in cases where ossicular plasty was necessary, a partial ossicular prosthesis was installed . Depending on the type of ossicular chain defect, the experience and preference of the surgeon, the choice of prosthesis used for reconstruction, was carried out (Matthew M. D .2020; H. Kawano et al. 2010) .

In the postoperative period, some patients experience a recurrence of hearing loss due to re-fixation of the stapes because of the scar growth tissue or ossification, serious complications such as floating footstool, labyrinth and damage of facial nerve (M. Sanna et al., 2003; BedriE-H, TeferiN., 2018; AntonelliPJ.et al., 2018) .

At re-fixation of stapes, which requires repeated surgery, the footplate of stapes is perforated and a piston-type prosthesis is installed (Vincent R., Oates J., Sperling N. M. 2002). The stapedoplasty at TSC shows excellent results in the postoperative period, but then with an

increase in ABG, the magnitude of which does not depend on the type of prosthesis, hearing deteriorates a little .

The presence of tympanic membrane perforation dictates myringoplasty, and only then the second stage to perform stapedotomy, after the formation of the neo- tympanic membrane (Chernushevich I. I. 2010; M. M. Dedmon et al. 2003) .

In the absence of incus, it is impossible to install a piston-type prosthesis; in this case, the stapedotomy ectomy is performed, and the oval window is closed with an auto-venous graft and the complete ossicular prosthesis is installed (A. Bayazit et al., 2004; Berenholz L., Lippy W. H., 2004). In order to minimize surgical trauma and complications during manipulations at the base of the stapes, the authors prefer stapedotomy. H. Kawano et al. (2010) notes the direct correlation between the size of perforation during stapedotomy and hearing loss at high frequencies.

According to other authors (H. Celik et al., 2008), the type of prosthesis used and the type of intervention performed do not affect the functional results of surgery. At the type of prosthesis used and the type of intervention performed does not affect the functional results of surgery. If it is impossible to mobilize the auditory ossicles, which is typical for the obliterating form of TSC, the alternative is to create the third window in the cochlea and install the vibration transmitter (Pau H. W., Just T.2010). If the functional outcome is ineffective after 3-4 repeated surgical interventions, the patient is recommended to undergo hearing aid implantation with a Vibrant Sound bridge hearing aid .

Despite the successful results of surgical intervention, re-fixation of the auditory ossicles is often noted in the long-term postoperative period (M. Forseni et al., 2002). The main reasons for the failure of tympanic plasty during TSC are considered to be displacement of ossicular prosthesis and re-fixation of the auditory ossicles by formed scars .

For the purpose of rehabilitation therapy in the postoperative period, it is recommended to use enzyme preparations such as hyaluronidase, lidase and ronidase to suppress adhesive processes in the tympanic cavity . Hyaluronidase breaks down the specific substrate - hyaluronic acid,

which is a “binding” substance of connective tissue, which causes the softening of scars (J. Vicente et.al.2006). The researchers recommend to introduce the enzyme preparations into the middle ear through the auditory tube by catheterization or electrophoresis; this procedure is recommended before and after surgery. Particular attention should be paid to the fact that hyaluronidase and its derivatives do not have prophylactic effect and do not prevent the formation of scar tissue, but act on already formed scar tissue .

During the removal of TSC foci, the mucous membrane of tympanic cavity was certainly injured, which contributed to the formation of scar tissue. The damage of mucosal tissue initiates repair processes, where fibrinogen effusion from the damaged vascular bed is first noted, followed by formation of insoluble fibrin matrix (P. A. Krovin et al. 2019). Accordingly, the larger the wound surface, the more fibrin falls out, the natural process of fibrinolysis is hampered by insufficient drainage and ventilation functions of the auditory tube (Patyakina O.K., 2002; Hashimoto S.A., 2000; Khan I., Jan A.M., Shahzad F., 2002) .

The attempts have been made to close the medial wall of tympanic cavity with fragments of the buccal mucosa in order to reduce the amount of fibrin released. In other cases, teflon or silicone are used instead of an autograft plates, but this method has its drawbacks, since it requires additional intervention after 5-6 months in order to remove artificial prostheses, to avoid the formation of connective tissue capsule around them, which certainly leads to limited mobility of the auditory ossicles (Tos M. 2004). The experimental studies conducted by Russel J. D., et al. (2002) showed the high efficiency of polydioxan one films, the advantage of which is the ability to dissolve within six months after surgery .

The formed fibrin matrix has an increased ability to adhere, that is, sticky. For this reason, when matrix-coated surfaces come into contact, they stick together, which leads to formation of adhesions in this area. Taking into account this mechanism of adhesions formation, as well as the possibility of the fibrin matrix being located on both damaged and intact surfaces, various preventive measures are used to prevent ossicular re-fixation .

Immediately after surgery, the release of fibrinogen from the vascular bed and the formation of a fibrin matrix begins, and this process continues for 3-5 days (S. Atmaca et al.2008). If fibrinous adhesions do not resolve, on the 2-3rd day fibroblasts begin to produce collagen fibers, and they acquire a fibrous structure.

By the end of the first week after surgery, the fibrin matrix is replaced by granulation tissue, and there is histologically can be found only fibrin residues. By the end of the second week the fibrin is completely absorbed and commissures are transformed into loose connective tissue, where the collagen fibers and blood vessels are identified. The germination of capillaries and nerve fibers can be observed from 7 to 21 days after surgery, by which time the process of epithelization of the surface of the adhesions have completed. Subsequently, the collagenization of scar tissue in the tympanic cavity increases, and foci of petrification and ossification appear .

Combining of specialized literature data:

Based on the foregoing, it can be affirmed, that, despite the significant number of comprehensive studies, including morphological and immunological, the issues of pathogenesis, treatment and rehabilitation of tympanic sclerosis have not been fully studied.

TSC is characterized by nonspecific degenerative-dystrophic process in the connective tissue structures of middle ear, which can occur in any chronic inflammation; at the same time, there is no systematization of data on morphological changes depending on the diseases forms.

Many factors play a role in the development of TSC - circulatory disorders, increased vascular permeability, immune imbalance and impaired metabolism of connective tissue proteins, but the mechanism of TSC relapse and the place of immune imbalance in its development have not been studied.

Despite the detailed technique of tympanic plasty and its successful implementation, in the long term there is often some functional deterioration that does not meet the expectations of both the patient and the doctor.

For this reason, optimizing the tactics of surgical treatment for patients with TSC, the work out methods of postoperative rehabilitation therapy, taking into account immunological and metabolic imbalances, are priority tasks, the solution of which has great scientific and practical importance.

CHAPTER II. MATERIALS AND METHODS OF RESEARCH

§2.1. The clinical characteristics of examined patients

Dissertation research was carried out at the clinic of Happy Life LLC medical center, TashPMI and at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, for the period 2019 - 2021. The clinical study covers 66 patients with tympanic sclerosis (nosological forms of disease H-74.0) aged from18 to 69 years.

The data of 437 patients with CPOM, who applied to the Happy Life LLC clinic for surgical treatment with a diagnosis of "chronic purulent otitis media" or "tympanic sclerosis in remission stage, were analyzed. In almost all cases, the diagnosis tympanic sclerosis was made during surgery, using oto-microscopy data, or was an intraoperative finding. It should be noted that the number of female patients prevailed, the proportion of which was 45 (68.18%) patients, against 21 (31.81%) male patients.

Criteria for inclusion in the study:

1. The patient's age at the time of inclusion in the study was defined as not less than 18 years and not more than 70 years;
2. The presence of complaints, medical history and local symptoms characteristic of long-term hearing loss;
3. At the time of the initial examination by oto-scopy, and then by oto-microscopy, signs characteristic of tympanic sclerosis must be determined;
4. At the time of examination there are no signs of acute inflammatory disease of other organs and systems;
5. Absence of conditions that limit the use of treatment methods used in the work.

6. Presence of typical oto-scopic symptoms (perforation, calcification with intact tympanic membrane) and without signs of acute inflammation

In the present study, the number of female patients prevailed (45; 68.18%), in previous studies the inverse ratio of men and women was observed - 2/3.

All patients were concerned about hearing loss at the time of treatment.

Depending on the contents of tympanic cavity, the patients were divided into 3 groups (Table 1):

Group 1 – 18 patients with limited tympanic sclerosis;

Group 2 – 26 patients with widespread tympanic sclerosis;

Group 3 - 22 patients, whose oto-microscopy revealed tympanic sclerotic calcified plaques in parallel with granulations, with desquamated epidermis, mucusitis and cholesteatoma.

§ 2.2. Examination methods

The thorough survey of each patient, clarifying the medical history and life history, was the integral part of the research. When interviewing patients, the complaints related to ear pathology (hearing loss, otorrhea, noise, buzzing in the ear, dizziness, cephalgia) were found out. In addition, the duration of disease, the causes of its occurrence, the frequency of exacerbations, information about previous conservative and surgical treatment, previous and concomitant diseases were also taken into account

.

Clinical examination

Before hospitalization, the patients were undergone general clinical tests (general blood count, determination of blood group and Rh factor, biochemical blood test to determine the level of glucose, bilirubin, alanine aminotransferase and aspartate aminotransferase; blood test for markers of hepatitis B and C, HIV, RW, coagulogram), MSCT of the temporal bones, presented data from chest radiography and electrocardiography,

after which they were sent for consultation to therapeutist and anesthesiologist.

Otorhinolaryngological examination

All patients were undergone a standard examination of ENT organs - anterior and posterior rhino-scopy, pharyngo-, laryngo- and oto-scopy. In all cases without exception, otoscopy was supplemented with otomicroscopy; during otoscopy, the condition of skin and diameter of external auditory ear passage, the type of tympanic membrane or its remains, the location and size of perforation, if it was there, the presence of pathological tissue (tympanic sclerotic spots, polyps, cysts, granulations, scars, cholesteatoma), the condition of mucous membrane of the tympanic cavity, the visible part of ossicular chain, were assessed. In patients who were undegone radical ear surgery, the visible parts of trepanation cavity were carefully examined and areas inaccessible for inspection were probed. In patients who had previously undergone tympanic plasty, the location and type of neo-tympanic membrane were analyzed and attention was paid to its mobility.

In addition to traditional examination, if necessary, the video endoscopic examination of nasal structures and nasopharyngeal formations was performed, paying special attention to the condition of the pharyngeal openings of the auditory tubes. The patency of auditory tubes was tested using various tests - with empty throat, Toynbee, Politzer and Valsalva. The patency of auditory tube was determined by tympanometry in case of perforation of the tympanic membrane.

Audiological examination

The audiological examination included acumetry, hearing testing with tuning forks, tone threshold audiometry in the standard and extended frequency range, and tympanometry.

The tone threshold audiometry (TPA) in the standard and extended frequency range was performed on audiometers AT-235 (manufactured by Interacousticus, Denmark) and GSi-61 (manufactured by Grason-Stadler, Inc., USA). The results of TPA were recorded in journals (fugure values) and on audiometric forms (graphically) for pasting into medical records. To assess hearing function, the average arithmetic value of the air and bone conduction thresholds of the tonal threshold audiogram, as well as the value of bone-air interval, using data for frequencies of 0.5, 1 and 2 kHz, . Changes in hearing function after surgery were recorded in the immediate (10-30 days) and long-term (3-12 months) periods, and compared with preoperative indicators.

The tympanometry was performed using AD-629 Interacoustics device (Denmark). The studies of biophysical parameters were carried out in semi-automatic and automatic modes in the form of recording tympanic metric curves, which were assessed using the J. Jerger classification .

The degree of hearing loss was established according to the unified international classification proposed by WHO in 1997 (Table 2.1) .

Table 2.1

Table of perceptual ability depending on the degree of hearing loss (WHO,1997)

Degree of hearing loss	Perception on threshold in decibels, dB	Speech perception ability
Normal	0-0,25 dB	Not difficult
Mild	26-40 dB	It is difficult to perceive quiet speech especially against background of noise or in large room, but communication in silence does not cause discomfort.

Average	41-55 dB	It is difficult to understand spoken language especially against background of noise. Increased volume is required when watching TV, radio or listening to music.
Medium-heavy	56-70 dB	The legibility is significantly reduced. The patient's speech is louder than usual, communication is significantly difficult in the classroom.
Heavy	71-90 dB	Conversational speech cannot be heard. Even loud speech is difficult to understand. Communication is only possible by shouting or using a heard aid.
Deep (deafness)	91+ dB	Even amplified speech is significantly difficult to perceive or impossible.

Radiation research methods

The multispiral computed tomography was performed at 66 patients on tomograph "Somatom Sensation 40" (Japan) in a spiral mode in axial projection with 3D reconstruction of bone tissue. The sections were made in 0.3 mm slices from the lower to the upper edge of mastoid process.

When performing MSCT, the attention was paid to the integrity of bone structures, the presence of pathological inclusions, their location and density by Hounsfield, and, also, structure, boundaries, shape, and state of adjacent soft, cartilaginous and bone tissues.

Surgical treatment of patients with tympanic sclerosis

The surgical intervention was carried out in one or two stages, the pathological formations were removed from the tympanic cavity, the ossicular chain was reconstructed and its mobility was restored, the myringoplasty was performed.

The surgery, in the prevailing cases, was carried out via post-uricular approach under general intubation anesthesia. In patients, who required reoperation, the endo-meatal and end-aural approaches were used. The reoperation was carried out to revise the tympanic cavity, to replace the auditory ossicular prosthesis, and to perform re-myringoplasty in patients who had the neo-tympanic membrane defect in the posterior quadrants.

The tactics of surgical treatment were carried out before surgery based on the anamnesis of disease, the results of otological and imaging studies with the volume of taking intervention, were finally determined after an audit of the middle ear structures, taking into account the localization and expressiveness of TSC foci, the presence of bone structures destruction, the mobility, the eardrum integrity and its mobility.

In order to improve the visibility of anterior meato-tympanic angle area, the plaques of the anterior wall were initially removed, widely separating the skin above it; this method was used when the frontal wall of external auditory canal was clearly protruded. If the external auditory canal is curved, there are performed the bone wedge-shaped resection of posterior and upper walls. Following the preparation of bed for transplant, the inspection and sanitation of middle ear were carried out, while all pathological formations and foci were removed (ingrown epidermis, polyps, purulent cysts, scars were dissected, the metaplastic mucous membrane of tympanic cavity was excised). When the TSC focus was localized in the thickness of tympanic membrane, the mobility of it and handle of malleus were impaired, or the focus was localized in the area of

the receptive bed for the fascial graft, the TSC foci were removed. If the ossicles were fixed in attic area, the anvil was removed and the head of malleus was resected. When immobilizing the stapes, the TSC lesions are removed to orbicular ligament, between the stapes crura, and until mobility is achieved. In the case of lesions localization on the tendon the stapedius muscle, tympanic sclerotic lesions were resected without affecting the tendon.

For reconstruct the chain of auditory ossicles, the partial and complete ossicular prostheses were most often used, less often stapes prostheses, the so-called pistons and prostheses of incus long leg. Mostly artificial implants were used - titanium or polymer. The prostheses made from cortical layer of temporal autologous bone were used only in 4 (6.1%) cases.

For myringoplasty, the auto-graft was used - fascia of temporalis muscle measuring 1-2.5 cm2, which was dried with a hairdryer and placed on the bone tympanic ring using the "underlay" technique. The graft was fixed by pressing it to the tympanic ring with silk threads 3-4 cm long, which were initially impregnated with petroleum jelly and iodine. The external auditory canal was packed with Merazel tampons. The operation was completed using the usual method - the surgical wound was sutured layer by layer and the aseptic bandage was applied.

Postoperative treatment

After completion of tympanic plasty and other types of surgical intervention, the patients were prescribed strict bed regimen up to 2 days, depending on the features of performed operation. Patients were placed sideways, with the operated ear facing upward. Then, for 3-4 days, the patients were advised to limit active and sudden movements.

In the postoperative period, the surgical wound was cared for, which consisted of changing and treating the sutures of the patient lying down, following the rules of asepsis and antisepsis in the surgical dressing room. The first dressing was done on the 1st-2nd day, depending on regimen prescribed to the patient. The next dressings of surgical wound take place at intervals of 1-2 days. The sutures were usually removed on

the 7-8th day, tampons from the external auditory canal were removed on the 25-28th day using pincers, micro-forceps and a surgical suction device with fine tip. On days 14-21 after surgery, after control oto-microscopy, 3% boric alcohol was dropped into ear per 1-2 times a day in order to reduce exudation and accelerate epidermization of the implanted eardrum. The anemization of mucous membrane in nose and nasopharynx, especially aimed at the area of pharyngeal opening of auditory tube, was carried out to improve ventilation of tympanic cavity and improve the outflow of wound discharge. The access was made through the lower nasal passage using long probe with cotton wool wrapped around it, soaked in 0.1% solution of adrenaline hydrochloride. The procedure was carried out daily, once a day, for 7-10 days. In order to optimize the function of auditory tube, the patients were recommended to chew gum per10-15 minutes twice a day for 15-20 days. At the same time, the gentle blowing of auditory tube was carried out by Politzer.

Postoperative rehabilitation therapy took an average of 1 to 2 months, which was continued until the cessation of exudation and epidermization of the neo-tympanic membrane.

Application of Longidase using ultrasound

To prevent postoperative relapses of tympanic sclerosis during the rehabilitation period the method of administering Longidaza using ultrasound – phonophoresis was worked out. When carrying out UST (UST-1.01 F-M) the Uzbek production drugs and equipment were used. In all groups, the traditional scheme of postoperative complex treatment (TSC) for the corresponding pathology was used.

Ultrasound (oscillation frequency 880 kHz - the lower the frequency, the deeper it penetrates into biological tissues) the physiotherapeutic treatment began after surgery on the 3rd day. After manipulations, the postoperative wound was bandaged.

The patient position during the ultrasound procedure is lying on his side. The localization of effect is the peri-temporal region. The contact is direct, contact medium dry substance of the drug “Longidaza 3000ME” was diluted immediately before procedure in 5.0-7.0 g. medical mineral

butter for ultrasonic exposure was applied on skin near the temporal region. The regimen of impulse power flux density mode was 0.4-0.7 W3. The impulse duration was 10 m., the technique was labile (movable) contact. The duration of the procedure is 10-15 minutes daily, once a day. The course of therapy includes 10 actions.

Low-frequency and mid-frequency ultrasound, due to the peculiarities of its absorption by biological tissues, more strongly change the vascular and epithelial permeability, has more pronounced loosening effect on tissue, which makes it possible to introduce more drugs and to greater depth with low-frequency UST compared to higher-frequency UST effects [Korkmazov M. Yu., 2015].

ultrasound and medications

Frequency 1 MHz Frequency 3 MHz Alternative frequency

1 MHz +3 MHz

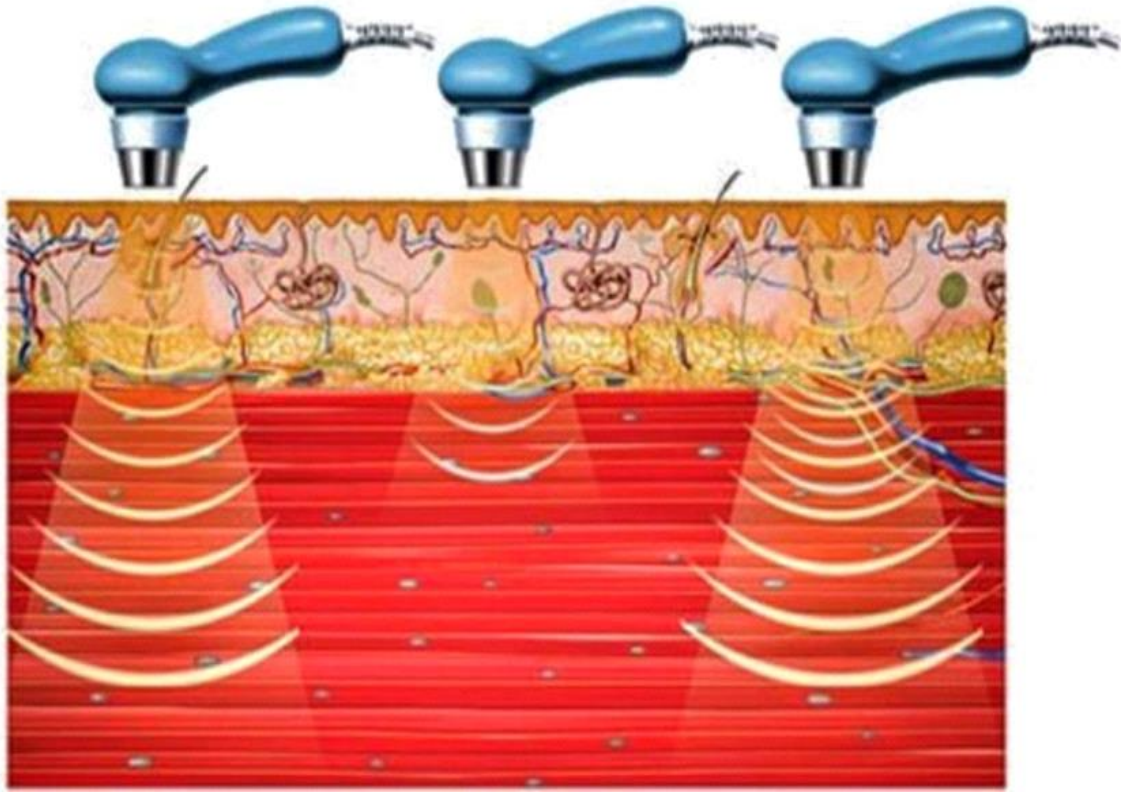


Fig.2.1. Effects of ultrasound and medications - ultraphonophoresis: high, small and medium doses of ultrasound.

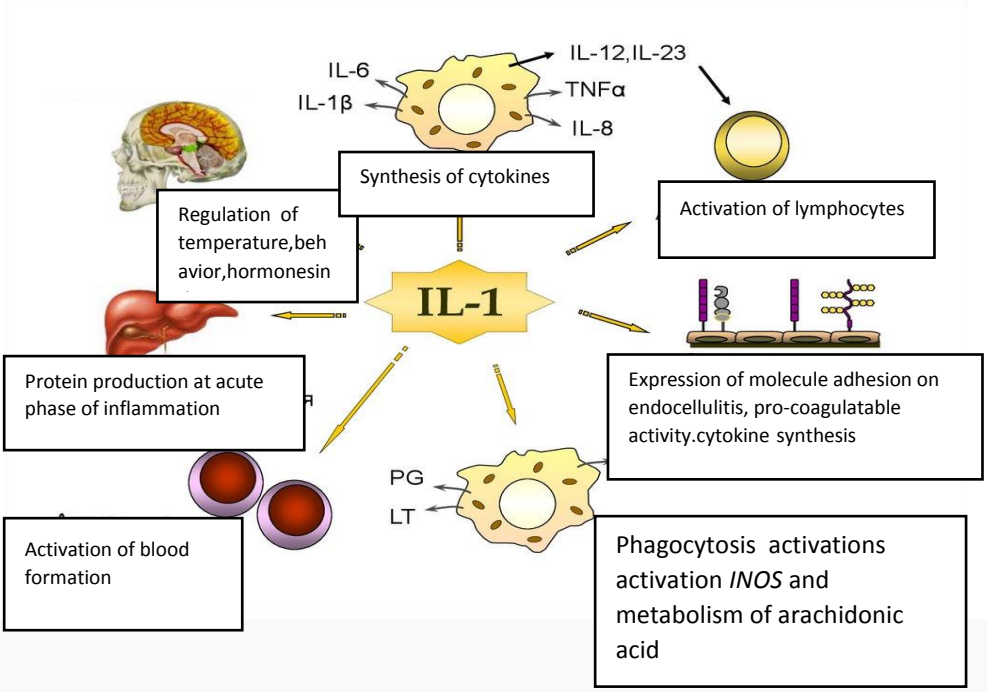
Determination of cytokine levels

Determination of cytokines level was carried out by immuno-ferment analysis (IFA) with study the level of interleukins IL-1β, IL-10 and IFNγ in blood serum and ear lavage. Blood samples for analysis were taken before and after complex therapy in volume of 5 ml from cubital vein. The ear lavage was collected before corrective measures. Then the eppendorfs with the test material were frozen in a freezer and stored at the temperature of minus 20°C until they were determined.

The determination of cytokine concentration in studied material was carried out using the three-stage "sandwich" method - a variant of a three-phase enzyme-linked immunosorbent assay, using mono- and polyclonal antibodies to the researching cytokines. The first stage consists of placing the test samples and standards into the wells of plate with immobilized antibodies. The cytokines in samples react with immobilized antibodies - interleukins and interferon (conjugate No. 1) and then interact during incubation with conjugate No. 2 (streptavidin with horseradish peroxidase). Using hydrogen peroxide (horseradish peroxidase substrate) and tetramethylbenzidine (chromogen), the amount of formed complex was determined by color reaction. The more intense the color (yellow color) of the sample, the greater concentration of studied substances in it. The resulting complexes are subjected to measurement of optical solution density in the wells, and, on the based reference samples with known concentration, the concentration of interleukins IL-1β, IL-10 and IFNγ in the studied samples were calculated.

IL-1β is the pro-inflammatory cytokine that plays a fundamental role in development of acute and chronic diseases. The same cytokine can act on many types of cells, causing different effects depending on the type of target cell. An example of the pleiotropic effect of IL-1 is presented in Fig. 2.2.

Fig.2.2. Pleitropic effect of IL-1. (D.S. Stashkevich 2016. pp. 8-9.)



The pro-inflammatory IL-1β plays an important role in inflammatory processes, both local and systemic. It is synthesized by many cells - fibroblasts, keratinocytes, stimulated B-lymphocytes and macrophages. The function of IL-1β is broad, it initiates and maintains the inflammatory response, promotes bone resorption, and promotes autoimmune processes. IL-1β increases the permeability of vascular wall, the activity of phagocytosis and chemotaxis, hematopoiesis, has cytotoxic and bactericidal activity, due to the activation of fibroblasts, stimulates collagen synthesis, and triggers a cascade of inflammatory-regulatory reactions [8,11].

The monitoring of IL-1-β content in the blood is a non-invasive and accessible research method that allows to assess the severity of inflammatory process.

Morphological study of surgical material

During the surgical intervention at patients with TSC the material for patho-morphological and histological examination was taken. The

histo-morphological study was carried out in the patho-morphological laboratory of IPSUM PATHOLOGY LLC, Tashkent.

The fixed material was dehydrated in increasing alcohol concentrations and then embedded in paraffin. The sections 5-6 mm thick were made from prepared paraffin blocks using a sled microtome, glued to fat-free glass slides, and stained with hematoxylin and eosin. The stained sections were embedded in polystyrene, covered with coverslips, and examined using a light microscope.

All histological sections were examined under a SOPTOP CX40P light binocular microscope (China) with a digital camera and an improved by Köhler lighting system. In all histological preparations the color, the nature of severity and extent of inflammatory process and physical density were assessed.

Statistical analysis methods

The statistical processing of research results was carried out according to generally accepted methods, after checking the data series for normality of distribution, using Microsoft Excel for Windows 2008 software packages, including the use of built-in statistical processing functions. The methods of various parametric and non-parametric statistics were used with calculation of average arithmetic mean (M), standard deviation (σ), standard error (m), relative values (frequency, %), the statistical significance of the obtained measurements when comparing average values was determined using the Student's test (t), with calculation of the probability of error (P) when checking the normality of distribution (by kurtosis test) and equality of general variances (Fisher's F test). The differences in mean values were considered important at significance level of $P<0.05$.

Conclusion to Chapter II

Thus, in order to fulfill the tasks assigned, 66 patients with tympanic sclerosis were examined, the selection was divided into 3 groups: 18 patients with limited form of TSC, 26 persons were with widespread form of TSC and 22 patients had TSC with cholesteatoma. The selection was

formed as a result of survey for 437 patients with COM(chronic otitis media). When compiling study groups, the inclusion and exclusion criteria were taken into account. The examined patients were undergone clinical, instrumental, immunological examination before and after proposed treatment methods. The anamnesis was studied to determine risk factors for the development of TSC in patients with COM. Oto-, rhino-, pharyngo-scopy, oto-microscopy were carried out in patients of study groups, MSCT of paranasal sinuses was performed in order to identify acute and chronic processes in them, as well as the presence of curvatures of nasal septum.

To determine the hearing loss degree, the tone threshold audiometry was performed.

To determine the state of local and general immunological status, the study of peripheral blood and ear lavage were carried out to study the content of IL-1β, IL-10 and IFN-γ.

The way of surgical intervention was described, during which the biological material was removed from sclerotic plaques and followed by histological examination of biomaterial. The methods of therapeutic and rehabilitation measures in postoperative period were described by using phono-phoresis with the Longidaza drug.

To establish the significance and reliability of data obtained the statistical research methods were carried out.

CHAPTER III. RESULTS OF CLINICAL AND AUDIOLOGICAL STUDIES OF PATIENTS WITH TYMPANIC SCLEROSIS

§ 3.1. Results of patients'clinical and otological examinations

The diagnosis of tympanic sclerosis was established at the preoperative stage and during surgery based, as a rule, on oto-microscopy data.

In the present study, attention was drawn to the clear predominance of women among patients, whose proportion was 45 (68.18%) patients.

Some studies report that female gender is a significant risk factor for the development of tympanic sclerosis, which is explained by frequent changes in hormonal levels in women at different periods of their life.

In the present study, attention was drawn to the clear predominance of women among patients, whose proportion was 45 (68.18%) patients.

Some studies report that female gender is a significant risk factor for the development of tympanic sclerosis, which is explained by frequent changes in hormonal levels in women at different periods of their life (pre-pubertal and pubertal age, pregnancy, lactation, menopause), as well as genetic factors and immunological reactions (Gibb A, Pang Y., 1994; Sinem Gökçe, 2019; Aisha Larem ., 2021 Nemati, Shadman, et al., 2022) .

In our studies, the duration of disease ranged from 2 to 25 years. All patients at the time of treatment were mainly concerned about hearing loss and some patients (62.1%) suffered from noise in the ears.

Depending on nature of changes and contents of tympanic cavity, the patients were divided into 3 groups (Table 3.1):

Table 3.1.

Distribution of patients by groups, age and gender

Groups	**1 group n=18**		**2 group n=26**		**3 group n=22**	
Gender	M	F	M	F	M	F
Quantity	8 (44,4%)	10 (55,6%)	8 (30,77%)	18 (69,2%)	5 (22,73%)	17 (77,27%)
Average age,years	27,7±3,1	27,9±1,7	28,3±1,9	35,6±2,8	36,8±3,5	34,6±3,3

Group I had 18 (27.3%) patients with limited tympanic sclerosis, whose tympanic sclerotic plaques were located in one area - on the eardrum, on the walls of tympanic cavity or on one of the auditory ossicles. Among them, there were 7 (38.9%) male and 11 (61.1%) female patients. The average age was 27.83±2.24 years (Me-27 years; min-18; max-54).

Group II had 26 (39.4%) patients with widespread tympanic sclerosis, involving the entire chain of auditory ossicles, the area of the oval or round window, tympanic cavity, cave or attic. Among this group there were 8 (30.8%) men and 18 (69.2%) females. The average age was 33.35±2.6 years (Me-32 years; min-18; max-62).

Group III had 22 (33.3%) patients with a mixed form of tympanic sclerosis with cholesteatoma, whose otomicroscopy revealed tympanic sclerotic calcified plaques in parallel with granulations, with desquamated epidermis, mycositis and cholesteatoma. The average age was 35.09±3.2 years (Me-35.1 years; min-18; max-69). The distribution of patients by gender and age is presented in Fig. 3.1.

The division into ten-year age groups was used.

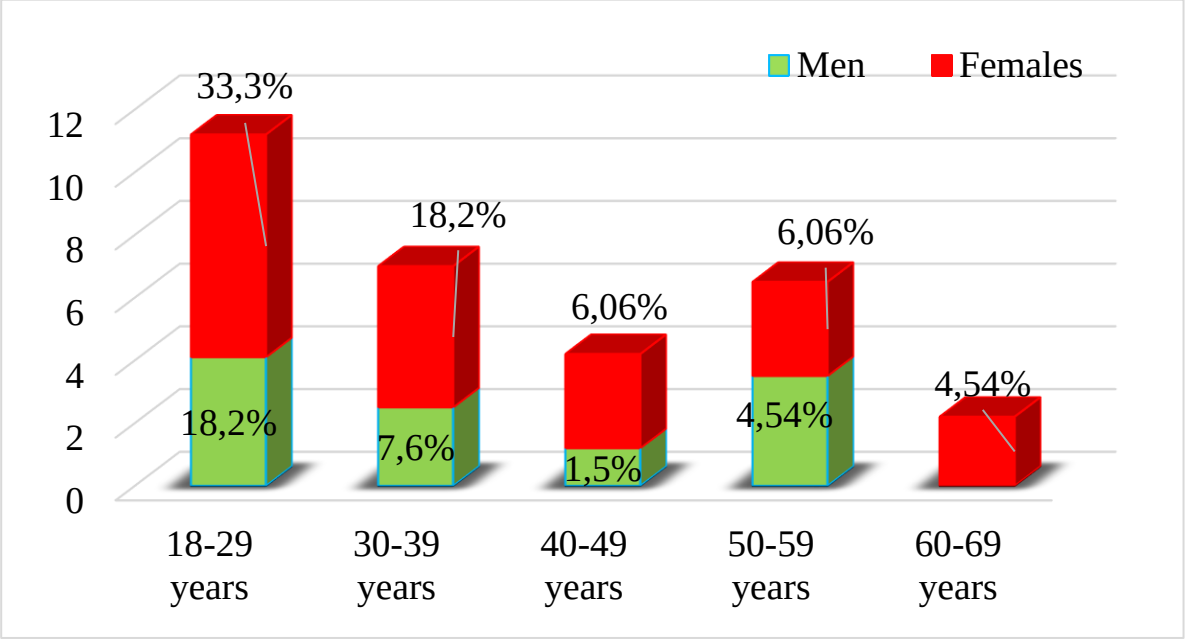


Fig.3.1. Age and gender characteristics of the examined patients (%).

The main peak of incidence occurred in the age group of 18-49 years - 84.8% of the total number of subjects, that is, young and middle-aged people, women of reproductive age, which is of great medical and social importance. Since it was during this period – the period the greatest vital activity and ability to work, there is the greatest need for socially adequate hearing, and, secondly, this can be explained by the fact that people of this age (31±7.4 years) often have limited economic opportunities for surgical hearing correction.

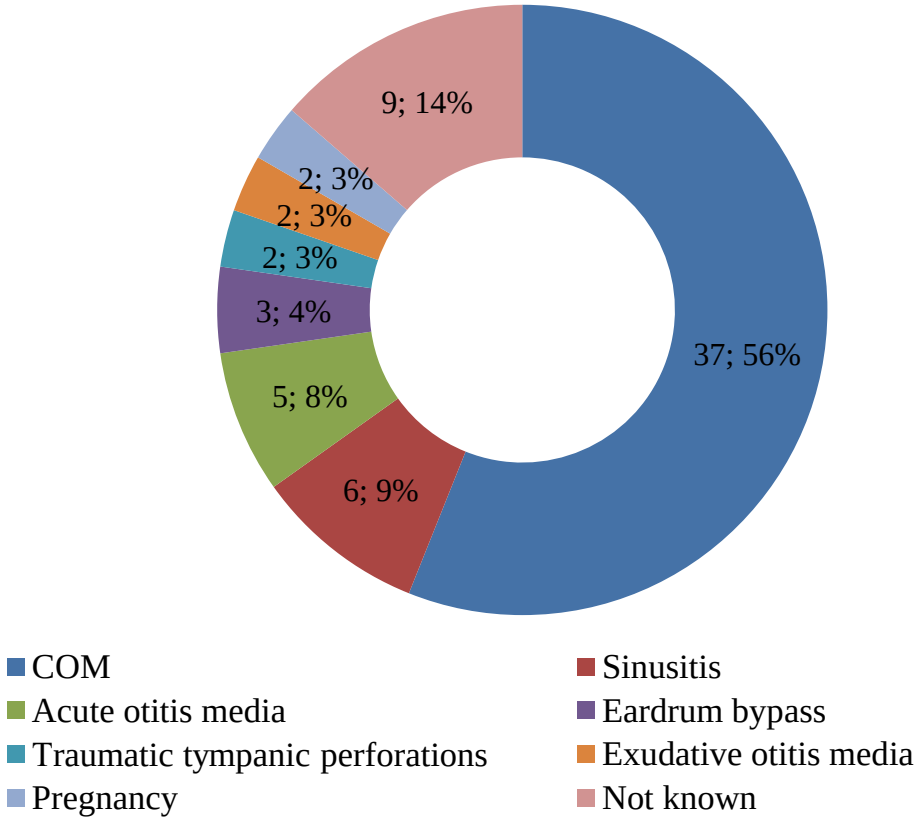
The bilateral pathological process was identified in 9 (50%) patients of group I, 9 (34.6%) patients of group II and 5 (22.7%) patients of group III. Unilateral ear lesions were present in 43 (65.1%), while the left-sided process was identified in 4 (22.2%) patients of group I, in 8 (30.8%) of group II and in 6 (27.3%) of group III groups. A right-sided process was detected in 5 (27.8%) patients of group I, 9 (34.6%) of group II and 11 (50%) of group III. The aspect ratio of TSC did not have statistically significant differences.

The analysis of anamnestic data showed that 11 (16.67%) patients had previously undergone surgical tonsillectomy, 7 (10.6%) patients had adenotomy for grade III adenoid vegetation, 6 (9.09%) patients had

undergone septoplasty, and 3(4.5%) of patients underwent bypass surgery of the tympanic cavity, 9 (13.6%) patients ever underwent puncture of the maxillary sinuses for acute and chronic sinusitis.

In the medical history, the majority (48; 72.7%) of patients reported that the pathology in question was preceded by acute otitis media. At the same time, 23 (34.8%) patients suffered acute otitis media before the age of 7 years, including 13 (19.7%) patients before the age of one year. In prepubertal age, 12 (18.2%) patients suffered from acute otitis media; untimely treatment and parental indifference led to a chronic form of otitis media.

As can be seen from Figure 3.2, chronic otitis media was the dominant etiological factor of tympanosclerosis (37; 56.1%). The development of TSC was preceded by acute otitis media in 5 (7.6%) patients; according to the patients, they noted a single episode of acute otitis media; they did not contact doctors for other ENT pathologies; for this reason, we associated TSC with the history of acute otitis media. In 7 (10.6%) patients, acute otitis media was a complication of an acute



respiratory viral infection.

Fig.3.2. Conditions preceding TSC

2 (3.03%) patients associate tympanosclerosis with injuries to the eardrum, 2 (3.03%) patients with secretory otitis, 3 (4.5%) patients associate this disease with shunting of the tympanic cavity, 2 (3.03%)) patients reported hearing impairment during pregnancy, while 9 (13.9%) patients did not associate the disease with anything, and the cause of TSC remained unknown.

Table 3.2.

Duration of tympanic sclerosis in the examined patients
1–3-rd groups (n=66)

Duration of tympanic sclerosis course	
up to 5 years 13 (19.7%)	13 (19,7%)
from 5 to 10 years old	16 (24,2%)
from 10 to15 years old	17 (25,8%)
from 15 to20 years old	11(16,7%)
More than 20 years old	9 (13,6%)

The duration of the disease (from the moment of hearing impairment and diagnosis) was up to 5 years in 13 (19.7%) examined patients, from 5 to 10 years in 16 (24.2%) patients, and in 17 (25.8%) patients. 10-15 years, in 11 (16.7%) patients 15-20 years, in 9 (13.6%) patients more than 20 years (Table 3.2).

In group III, patients with disease duration of up to 5 years old made up smaller percentage, patients with a disease duration of 5-10 years and more than 20 years made up a larger percentage compared to patients in groups I and II - 13.6%, 31.8% and 18.2% accordingly, but the difference in average values was statistically insignificant (Fig. 3.3).

The prevailing and often the only complaint in patients with tympanic sclerosis with or without fixation of the auditory ossicles was the complaint of hearing loss n=66 (100%). In approximately half of the cases, patients noted the presence of constant or periodically occurring

noise, humming in the affected ear (41; 62.1%) (Table 3.3.).The patients became anxious, because of, both frequent ear discharge (46; 69.7%) and episodic discharge (8; 12.1%). In 12 (18.2%) cases ,the discharge from the ear was not bother some patients. Complaints of pain, discomfort in the ear in the form of feeling of fullness in the affected ear, the feeling of fullness and pressure in the ear and/or parotid area on the affected side were present in every third patient (21; 31.8%), and pain in the ear was often dull and aching character, and intensified with physical and mental stress, coughing.

As can be seen from Table 3.3, the patients of groups II and III had more severe and pronounced clinical symptoms. Thus, noise in the ear of a periodic nature was recorded significantly in a larger number of patients in group II (18; 69.2%) compared to group I (6; 33.3%) (P<0.02). In 14 (77.8%) patients of group I, discharge from the ear was mucopurulent in nature, which was significantly more than the number of patients in group II (P<0.02) and III (P<0.001). The purulent discharge in patients of group I was not detected, while in patients of group II (P<0.001) and group III (P<0.001) it was significantly prevailed. The fetid odor of discharge was statistically significantly higher in patients of group III relative to patients of group I (P<0.001) and group II (P<0.001).

Table 3.3.

Main complaints of patients in study groups (n = 66)

Patients complaints	**I group n=18**	**II group n=26**	**III group n=22**	**P_{1-2}**	**P_{1-3}**	**P_{2-3}**
Hearing loss	18 (100%)	26 (100%)	22 (100%)			
Noise in ear	8 (44,4%)	20 (76,9%)	13 (59,1%)			
- permanent	2 (11,1%)	2 (7,7%)	3 (13,6%)			
- periodic	6 (33,3%)	18 (69,2%)	10 (45,5%)	0,02		
Discharge from ear	14 (77,8%)	21 (80,8%)	19 (86,4%)			
- constant	-	1 (3,8%)	5 (22,7%)		0,02	

- about 2-3 times a year - several times a year - once every few years - no discharge	6 (33,3%) 5 (27,8%) 3 (16,7%) 4 (22,2%)	7 (26,9%) 11 (42,3%) 2 (7,7%) 5 (19,2%)	5 (22,7%) 8 (36,4%) 1 (4,5%) 3 (13,6%)			
Feeling of stuffiness in the sore ear	1 (5,6%)	3 (11,5%)	2 (9,1%)			
Feeling of fullness and pressure in ear	1 (5,6%)	3 (11,5%)	1 (4,6%)			
Difficulty understanding speech	1 (5,6%)	2 (7,7%)	2 (9,1%)			
Character of discharge: - purulent - mucopurulent	- 14 (77,8%)	10 (38,5%) 11 (42,3%)	14 (63,6%) 5 (22,7%)	0,001 0,02	0,001 0,001	
Discharge - with smell - odorless	- 14 (77,8%)	3 (11,5%) 18 (69,2%)	14 (63,6%) 6 (27,3%)		0,001 0,001	0,001 0,002
Pain near mastoid process, otalgia	1 (5,6%)	6 (23,1%)	11 (50%)		0,001	
Pain in the neck on the side of affected ear	-	1 (3,8%)	1 (4,6%)			
Nausea	-	1 (3,8%)	1 (4,6%)			
Vomiting	-	-	2 (9,1%)			
Headache	3 (16,7%)	9 (34,6%)	12 (54,6%)		0,01	
Dizziness	1 (5,6%)	5 (19,2%)	4 (18,2%)			
Facial assymetry	-	1 (3,85%)	1 (4,6%)			

There was no pain in the mastoid region in patients of group I, however, there were significantly more patients experiencing pain in the

mastoid region among patients in group III (P<0.001). Also, there were significantly more patients experiencing ear pain (P<0.02) and headache (P<0.01) in group III compared to patients in group I.

Patients of group II noted pain in the neck on the side of the affected ear (1; 3.8%), local pain in the mastoid region (3; 11.5%), pain in the ear (4; 15.4%), headache pain (9; 34.6%), manifestations of vestibular dysfunction in the form of dizziness (5; 19.2%), nausea (1; 3.8%).

Among patients of group III, pain in the neck on the side of the affected ear (1; 4.6%), pain in the mastoid region (7; 31.8%), pain in the ear (8; 36.2%), and headache were observed. more than half of the patients (12; 54.6%), dizziness (4; 18.2%), nausea (1; 4.6%) and vomiting (2; 9.1%).

Table 3.4

Frequency of patient complaints depending on the duration of the disease

Complains of patients	**under 5 years old n=13**	**from5 to10 years old=16**	**from10to 15 years old n=17**	**from15to 220 years old n=11**	**> 20 years old n=9**
Hearing loss	13(100%)	16(100%)	17(100%)	11(100%)	9 (100%)
Noise in ear:					
- permanent	2 (15,4%)	2 (12,5%)	1 (5,9%)	2 (18,2%)	-
- periodic	4 (30,8%)	10 (62,5%)	10 (58,8%)	3 (27,3%)	7 (77,8%)
Discharge from ear	9 (69,2%)	11(68,7%)	17 (100%)	8 (72,7%)	9 (100%)
- constant	1(7,7%)	1 (6,3%)	2 (11,8%)	2 (18,2%)	-
- several times a year	2 (15,4%)	3 (18,7%)	9 (52,9%)	4 (36,4%)	6 (66,7%)
- about 2-3times a year	6 (46,2%)	5 (31,3%)	4 (23,5%)	2(18,2%)	1 (11,1%)
- once every few years	1(7,7%)	1 (6,3%)	2 (11,8%)	-	2 (22,2%)
- no discharge	3 (23,1%)	6 (37,5%)	-	3(27,3%)	-
Feeling of stuffiness in the store ear	-	1(6,3%)	2 (11,8%)	2 (18,2%)	1 (11,1%)

Feeling of fullness and pressure in ear	3 (23,1%)	1(6,3%)	-	1(9,1%)	-
Difficulty understanding speech	1(7,7%)	1(6,3%)	2 (11,8%)	1(9,1%)	-
Character of discharge : - purulent - mucopurulent	4(30,8%) 6 (46,2%)	5 (31,3%) 5 (31,3%)	6 (35,3%) 11(64,7%)	4(36,4%) 4(36,4%)	5 (55,6%) 4 (44,4%)
Discharge - with smell - odorless	1(7,7%) 9 (69,2%)	4 (25%) 7 (43,7%)	4 (23,5%) 13(76,5%)	4(36,4%) 4(36,4%)	4 (44,4%) 5 (55,6)%
Pain near mastoid process, otalgia	3(23,1%)	6 (37,5%)	3 (23,1%)	4 (36,4%)	2 (22,2%)
Pain in the neck on the side of affected ear	1(7,7%)	-	-	1 (9,1%)	-
Nausea	1(7,7%)	1(6,3%)	-	-	-
Vomiting	1(7,7%)	1(6,3%)	-	-	-
Headache	6 (46,2%)	6 (37,5%)	6 (35,3%)	3(27,3%)	3 (33,3%)
Dizziness	3 (23,1%)	1(6,3%)	3 (17,6%)	2 (18,2%)	1 (11,1%)
Facial assymetry	1(7,7%)	-	1(5,9%)	-	-

As it can be seen from the table above, with a long course of the pathological process (more than 5 years), along with progressive hearing loss, symptoms such as tinnitus, humming, poor speech intelligibility, facial asymmetry, etc. are observed. These symptoms dominated in the TSC group with cholesteatoma.

According to the classification, Gibb A.G., Pang Y.T. (1994), we determined the type of tympanic sclerosis, which is based on the condition of the eardrum - integrity or lack thereof (Fig. 3.4)

Patients of group II noted pain in the neck on the side of the affected ear (1; 3.8%), local pain in the mastoid region (3; 11.5%), pain in the ear (4; 15.4%), headache pain (9; 34.6%), manifestations of vestibular dysfunction in the form of dizziness (5; 19.2%), nausea (1; 3.8%).

Among patients of group III, pain in the neck on the side of the affected ear (1; 4.6%), pain in the mastoid region (7; 31.8%), pain in the ear (8; 36.2%), and headache were observed. more than half of the patients (12; 54.6%), dizziness (4; 18.2%), nausea (1; 4.6%) and vomiting (2; 9.1%).
Picture 3.4. Type of tympanosclerosis according to Gibb A.G., Pang Y.T. (1994) in patients of the study groups (%).
Otomicroscopic examination data showed the presence of central perforation of the tympanic membrane in 27 (40.9%) patients, subtotal perforation in 16 (24.2%) patients, total perforation in 15 (22.8%) patients, and no perforation of the tympanic membrane was observed in 8 (12.1%) patients (Table 3.5.).

Table 3.5.

Localization of perforation of the tympanic membrane in patients of the study groups

Localization of perforation	**I group n=18**	**II group n=26**	**III group n=22**	**Total**
Central	12 (66,7%)	9 (34,6%)*	6 (27,3%)*	27 (40,9%)
Subtotal	3 (16,7%)	5 (19,2%)	8 (36,4%)	16 (24,2%)
Total	3 (16,7%)	7 (26,9%)	5 (22,7%)	15 (22,8%)
Without perforation	-	5 (19,2%)*	3 (13,6%)	8 (12,1%)

Note: *-P<0,05 difference is significant relative to group 1.

There were 23 (34.8%) patients with bilateral ear lesions, and 43 (65.2%) patients with unilateral lesions. During otoscopy, mucopurulent discharge in the external auditory canal was found in 30 (45.5%) patients, thick purulent discharge like condensed milk in 24 (36.4%) patients, of which 17 (25.75%) had a foul odor . The presence of cholesteatoma masses was determined in 12 (18.2%), tympanosclerotic plaques in 13 (19.7%) patients, clearly visible granulation was detected in 7 (10.6%) people.

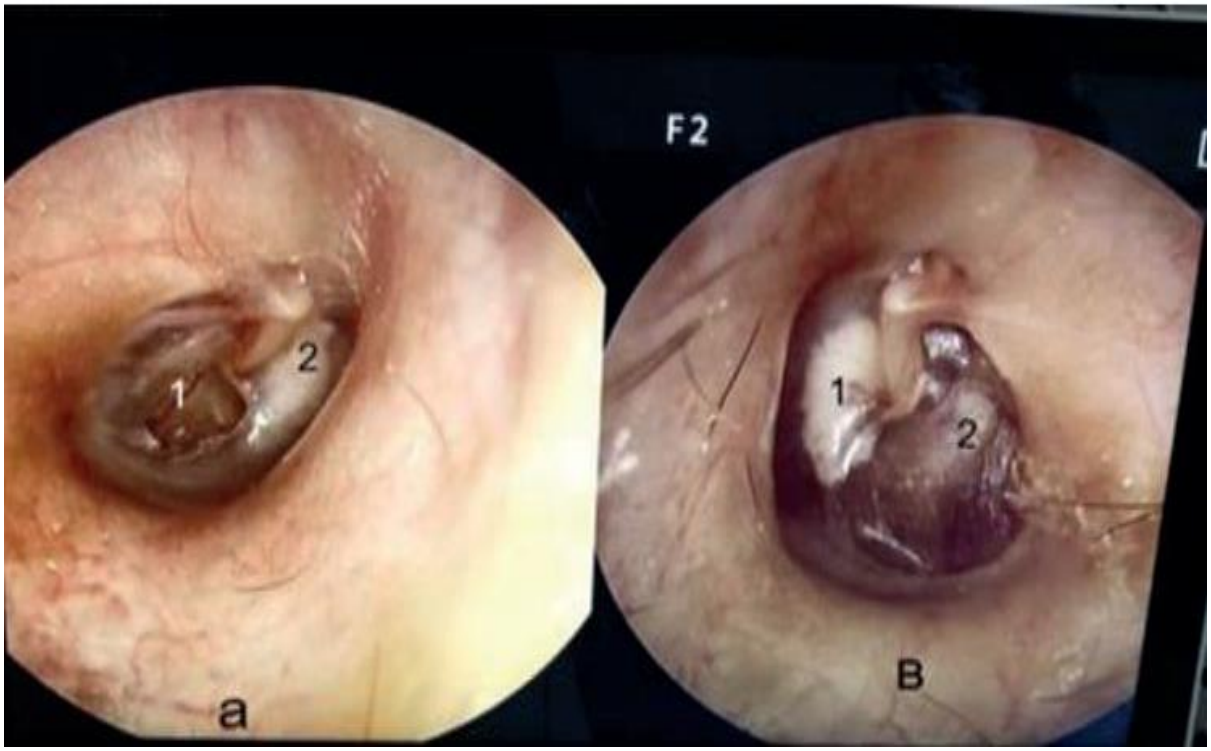


Fig. 3.5.a. Patient N., 24 years old. Open form of tympanic sclerosis Disease duration is 15 years. Oto-microscopic picture: 1) perforation, 2) calcification.

Fig.3.5.c. Patient X., 45 years old. Closed form of tympanic sclerosis. The duration of the disease is 11 years. Oto-microscopic picture: 1) large areas of hard calcified spots on the eardrum. 2) calcification, white pearl beads.

Fig. 3.6.a. Patient I.R., 29 years old. Closed form of tympanic sclerosis Disease duration: 2 years. Oto-microscopic picture (bean-shaped).Fig. 3.6.v. Patient F.Sh., 31 years old. Closed form of tympanic sclerosis. The duration of the disease is 5 years. Oto-microscopic picture (island-shaped) of diverse tympanic sclerosis crystals.

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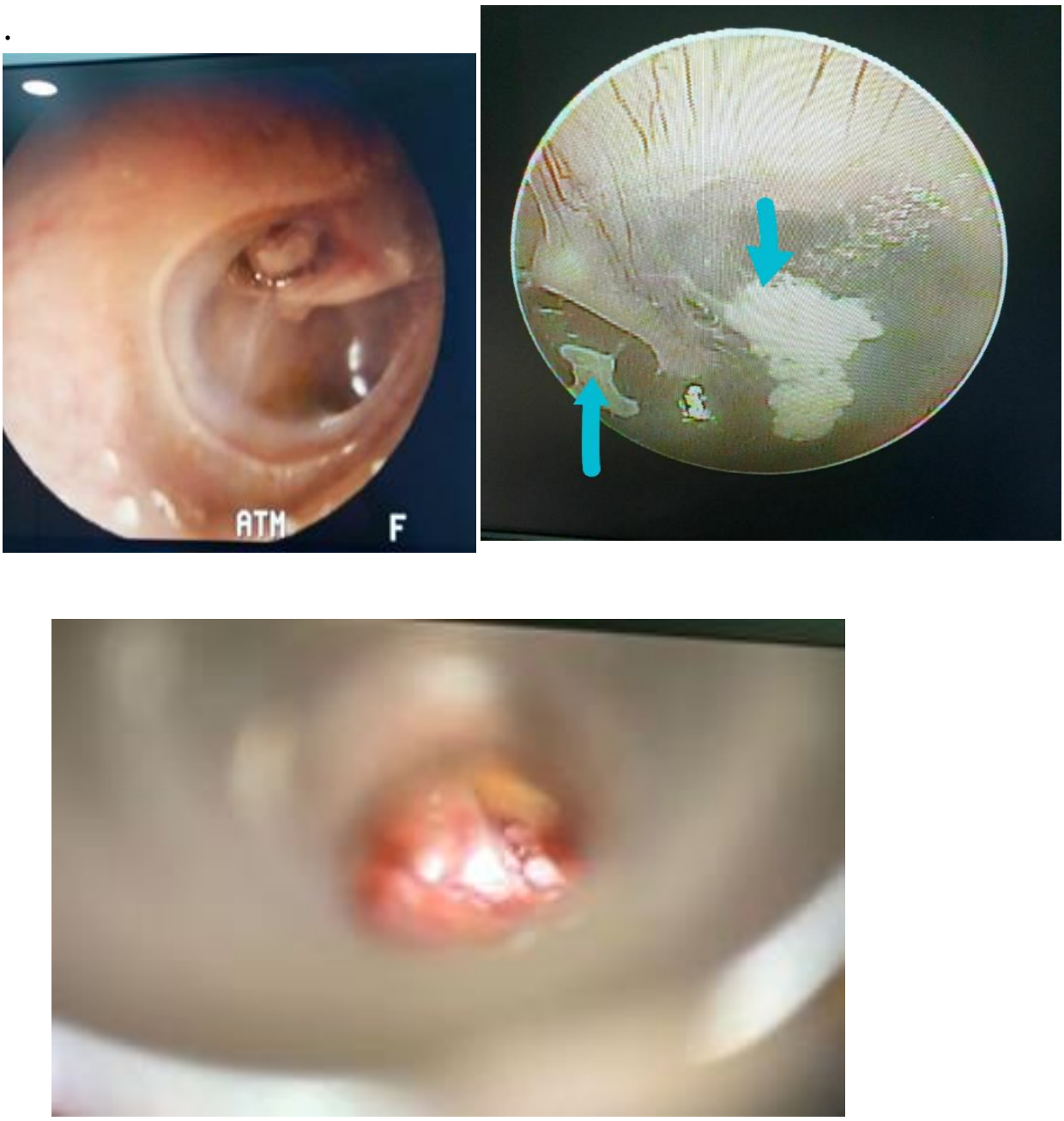

Fig. 3.6.s. Patient A.M., 39 years old. Open form of tympanic sclerosis (round, oval and crescent-shaped, bead-shaped). The duration of the disease is 15 years. Oto-microscopic picture: calcifications on the eardrum in the form of white pearls.

The results of oto-microscopy before surgery and during the intervention revealed polymorphism of changes in the tympanic membrane and the tympanic cavity - in some patients behind the tympanic membrane we

found whitish, oval, spherical, bean-shaped, and even TSC pearl-like plaques of various sizes (Fig. 3.5., 3.6.). TSC pearl-like plaques were more often found in the group with the common form of TSC (Fig. 3.5-3.6)

The results of anterior rhinoscopy showed the presence of symptoms of acute and chronic inflammation of the mucous membrane of the upper respiratory tract in 7 (10.6%) patients, which were manifested by hyperemia and swelling of the mucous membrane of the nasal cavity and inferior turbinate. Severe curvature of the nasal septum was detected in 22 (33.3%) patients (S and F shaped), hypertrophy of the anterior and posterior ends of the inferior nasal turbinates was detected in 5 (7.6%) cases. Pharyngoscopy showed the presence of local signs of chronic tonsillitis in 26 (39.4%) patients (liquid caseous plugs of Zach, Giese and Preobrazhensky), in 6 (9.09%) patients hypertrophy of the palatine tonsils of the I-II degree.

According to the results of MSCT of the temporal bones, in patients who took part in the study (n=66) and suffering from CHC with TSC with varying duration of the disease, the mastoid process had varying duration of the disease, the mastoid process showed signs of a sclerotic and destructive process. In 27 patients (41%), carious lesions of the middle ear cavity and bone, as well as the facial nerve canal, were detected. In 33.3% of cases (22 patients), the tympanic cavity, aditus and antrum partially or completely consisted of a homogeneous pathological substrate and soft tissue formation (density 56.2±1.3 units). In all cases, no changes in the structure of the inner ear were found.

§ 3.2. Results of preoperative audiological examination

According to the results of pure tone threshold audiometry performed on all patients in the study groups, a mixed form of hearing loss was identified in 56 (84.8%) patients, a conductive form in 9 (13.6%) and a sensorineural form of hearing loss in 1 (1.5%) patient (Fig. 3.6).

The presence of only a conductive component of hearing loss in patients can be explained by the location of the TSC plaques; they were located only on the tympanic membrane, without involving the ossicular chain;

the perforations of the tympanic membrane were small; cavities. The duration of the disease in these patients was no more than 2 years.

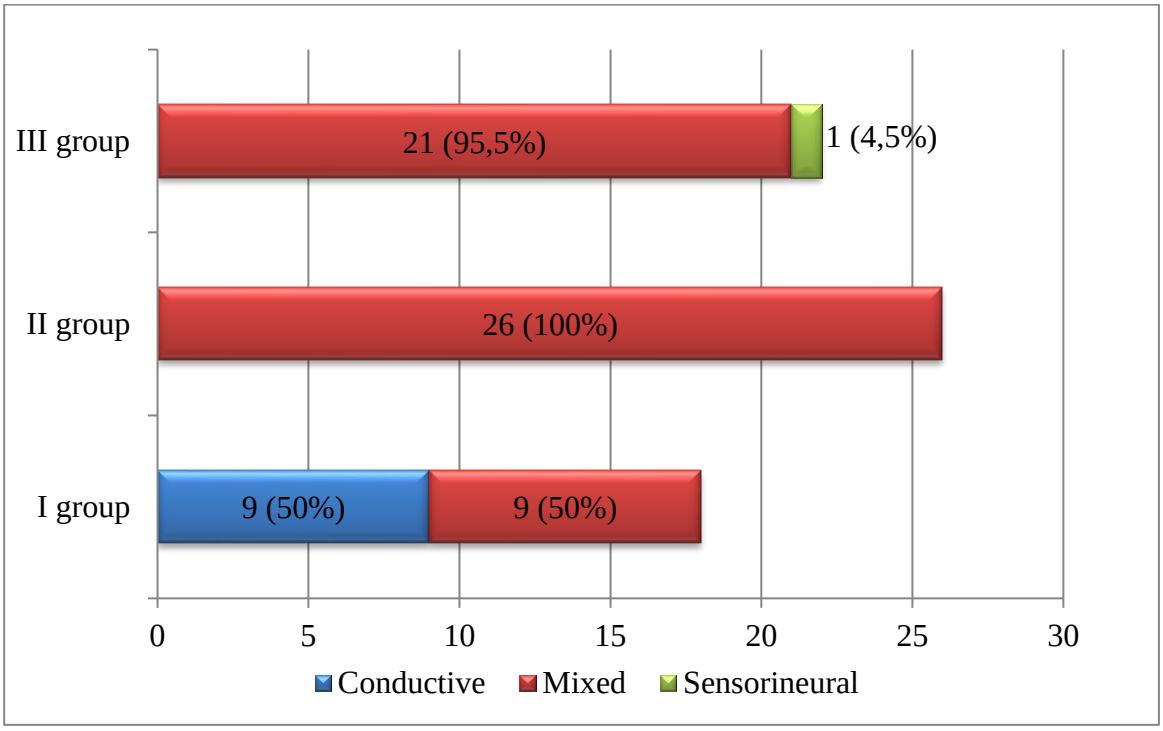

Fig. 3.6. Forms of hearing loss at patients of study groups

The degree of hearing loss varied at patients with tympanic sclerosis from I to IV level(Fig.3.7)

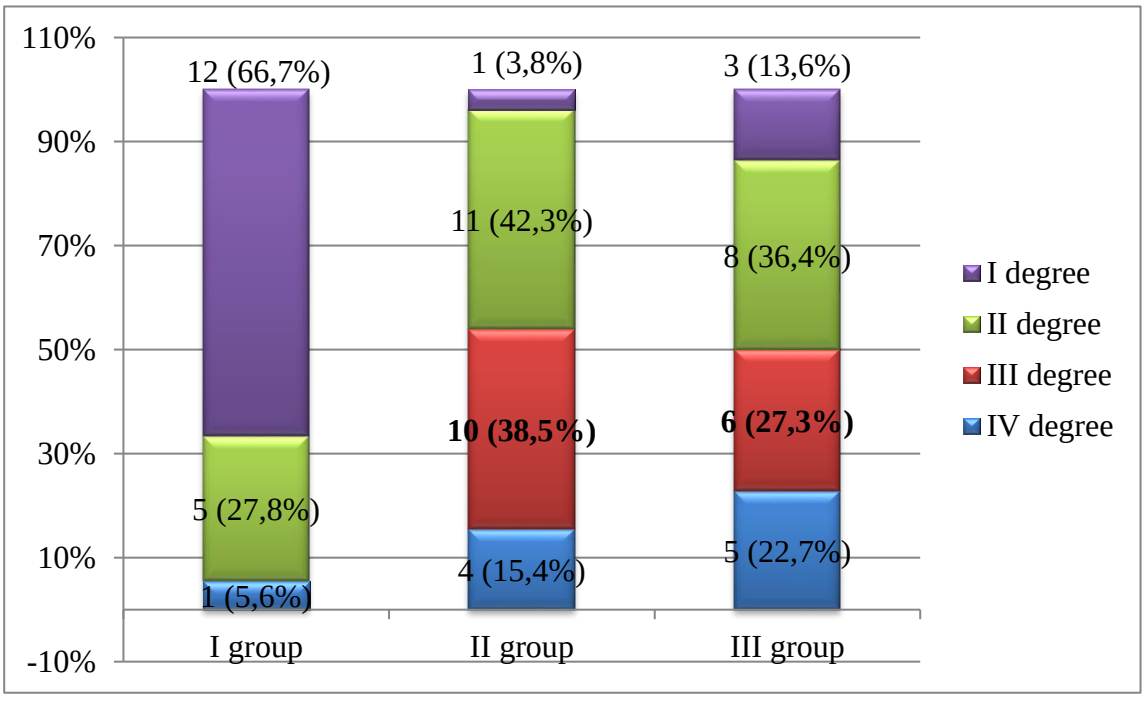

Fig.3.7. Distribution of patients depending from degree of hearing loss.

Degree I hearing loss was detected in 16 (24.2%) patients, while this degree of hearing loss was statistically significantly more prevalent in group I patients relative to patients in groups II (P<0.001) and III (P<0.005). The average value of hearing thresholds was 33.0±0.88 dB.

Degree II hearing loss was determined in 24 (36.4%) patients; the difference in the number of patients with this degree of hearing loss between the study groups was statistically insignificant. The average hearing threshold was 48.4±0.95 dB.

Hearing loss of the third degree was detected in 16 (24.2%) patients, while patients with this degree of hearing loss were not identified in group I of the study, and the differences relative to groups II and III of the study were statistically significant, P <0.001 and P <0.01, respectively . The average hearing threshold was 62.4±1.4 dB.

In 74.2% of patients with an increase in the threshold of airborne sound conduction, corresponding to II-III degree of hearing loss on the audiogram performed before surgery, intraoperatively revealed damage to the ossicular chain, which has prognostic significance.

The proportion of patients with mild hearing loss (24.2%) totaled a quarter of the study population. On pure tone threshold audiometry in the study groups, the following values of hearing thresholds were determined depending on the forms of hearing loss (Table 3.6).

Table3.6.

TPA data in study groups depending on the forms of hearing loss

Forms of hearing loss	**I group**	**II group**	**III group**
Conductive	34,3±1,04	-	-
Mixed	43,56±3,29	57,7±2,23*	58,6±3,47**
Sensorineural	-	-	29,0
Total	38,9±2,6	57,7±2,23*	57,24±3,66*

Note: the differences of average values is true relatively to group 1. * - P<0,001; **-P<0,005.

As it is seen from the table the more severe degrees of hearing loss were revealed in II and III study groups.

Thus, in 9 (50%) patients of group I, the conductive form of hearing loss was determined and the hearing threshold in these patients was 34.3 ± 1.04 dB (min = 30 dB; max = 42 dB), while in the remaining 9 (50%) Patients in this group had a mixed form of hearing loss, and the hearing threshold in these patients was 43.56±4.5dB (min=28dB; max=74dB). Moreover, the difference in means was significant between these forms of hearing loss in this group (P<0.05).

In patients of group II, as can be seen from table. 3.6 and fig. 3.6 identified only a mixed form of hearing loss, and the tonal hearing threshold in these patients was 57.8±2.26 dB (min=31dB; max=77.5dB), which was significant relative to group I (P<0.001).

In patients of group III, a predominantly mixed form of hearing loss was also observed (21; 95.5%) and the hearing threshold of these patients averaged 57.24±3.66dB (min=29dB; max=100dB), which was significant relative to group I (P<0.001).

Conclusions to Chapter III

Frequent ARI (3-4 times a year), complicated by AOM, sinusitis (P<0.001), deviated nasal septum (P<0.001), chronic sinusitis (P<0.001), duration of CSO (P<0.001) were significant in the development of TSC. , as well as the gender of the patient (P<0.001) – female.

The clinical course of TSC with cholesteatoma and TSC of the widespread form was more severe compared to TSC of the limited form, which was manifested by a relatively large number of patients with purulent discharge from the ear (P<0.001), a large number of patients with a fetid odor of discharge (P<0.001), pain in the mastoid area (P<0.005), as well as the number of patients experiencing ear pain (P<0.02) and headache (P<0.01).

In patients with limited-form TSC, central localization of perforation of the tympanic membrane was significantly more often observed (P<0.05), and on otomicroscopy the sclerotic plaque had a softer consistency (P<0.05) relative to widespread TSC and TSC with cholesteatoma.

More severe degrees of hearing loss (grades II-V) were significantly more often observed in patients with widespread TSC and TSC with cholesteatoma relative to limited TSC ($P<0.05$). The tonal hearing threshold in patients of group II (57.8±2.26dB) and group III (57.89±3.87dB) was significantly higher relative to group I (38.9±2.6dB), the difference was statistically significant ($P <0.001$ and $P<0.001$, respectively).

CHAPTER IV. RESULTS OF LABORATORY STUDIES IN PATIENTS WITH TYMPANIC SCLEROSIS

In recent years, the more and more new facts have appeared indicating the pathogenic connection of significant part of ENT-pathology with the state of immune system, in particular with the cytokine system (A.S. Simbirtsev, G.V. Lavrenova, 2018). The cytokines are direct participants in activation and regulation of the body's immune reactions, including local ones (Simbirtsev A.S., 2002).

Some data suggest that sclerotic changes in tympanic cavity, as a rule, develop the secondary acute and chronic otitis media and secretory otitis. That is, there takes place the chronic inflammatory process, at the result of which the hyaline and fibrin are formed, otherwise, the pre-conditions are created for the formation of sclerotic plaques. In this regard, it is interesting to study the content of some pro-inflammatory cytokines, both in systemic bloodstream and locally in the area of pathological focus, thereby, making it possible to determine the tactics of therapy and the point of impact for rehabilitation measures.

§4.1. Assessment of systemic cytokine status in patients with tympanic sclerosis

In connection with the above, there was carried out the study to research the level of pro-inflammatory (IL-1β) and anti-inflammatory (IL-10) cytokines, as well as the level of interferon-γ (INF-γ) in patients with various forms of tympanic sclerosis in blood serum.

In Fig. 4.1. the content of cytokines in blood serum of persons who made up the control group. As it can be seen from the presented data, the level of IL-1β in the blood serum averaged 27.16±0.89 pg/ml with range of individual values from 22.27 to 30.3 pg/ml. The level of IL-10 in the peripheral blood serum of individuals in the control group averaged 13.75±0.58 pg/ml with a range of individual data from 11.14 to 19.9 pg/ml.

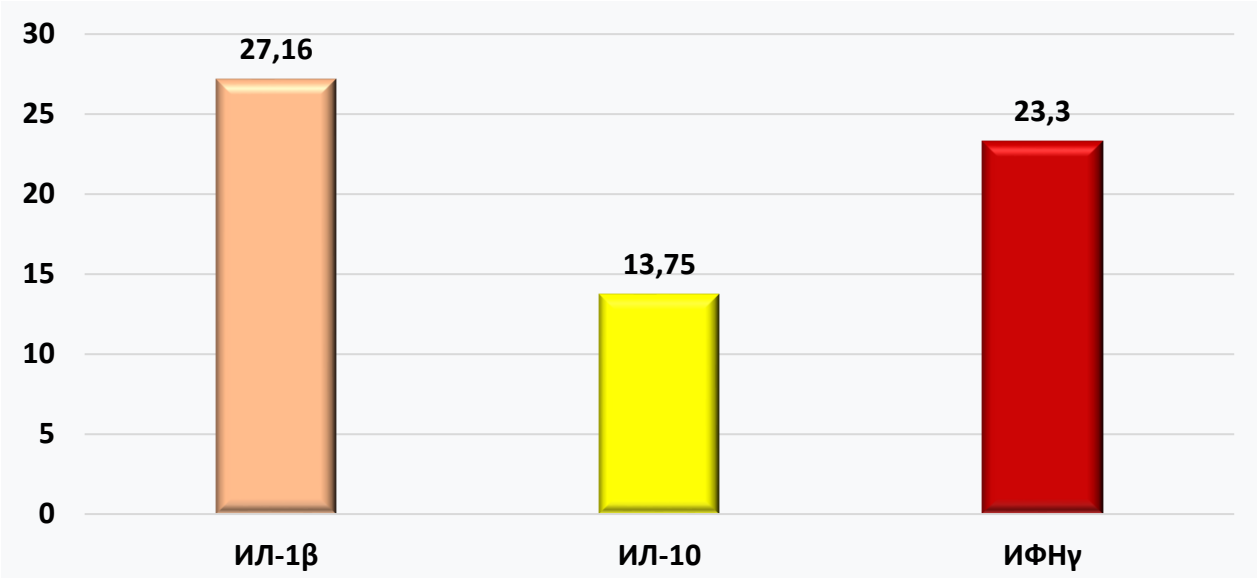

Fig.4.1. The serum level of cytokines and interferon-γ in the control group, pg/ml.

In our studies, in the group of individuals who made up the control group, the average IFN-γ level was 23.3±0.69 pg/ml with a range of individual values from 18.9 to 26.8 pg/ml (Fig. 4.1).

In patients with limited form of tympanic sclerosis, the level of IL-1β was 1.3 times lower than the values in the control group, and the average value was 20.59±0.94 pg/ml with the range of individual values from 15.2 to 25.4 pg/ml ml, (P<0.001). The induction of IL-1β synthesis in patients with limited form of tympanic sclerosis reflects the characteristics of inflammatory process. As it can be seen from data in Table 4.1, the level of IL-1β in patients with a common form of tympanic sclerosis was 1.2 times higher than the control data, averaging 32.5±0.6 pg/ml (27.2±0.9 pg /ml in control) with the range of individual values from 25.4 to 38.1 pg/ml. That is, a significant increase in the level of IL-1β in the blood serum was observed relative to the control group (P<0.001), relative to the group of (P <0. patients with a limited form of TSC 001).

Table 4.1.

The level of cytokines in examined patients with tympanic sclerosis, (pg/ml)

Groups	**IL-1β**	**IL-10**	**IFNγ**
Control group	27,2 ± 0,9	13,7 ± 0,6	23,3 ± 0,7
I group	20,6 ± 0,94*	25,7 ± 0,91*	29,9 ± 1,83**
II group	32,5 ± 0,6*#	19,3 ± 0,75*#	37,5 ± 0,91*#
III group	37,8 ± 0,85*#^	21,4 ± 0,6*#^^	35,5 ± 1,02*##

Note: Values are significant relative to the control group data *P<0.001; **P<0.002; significant relative to group 1: #- P<0.001; ##- P<0.02; significant relative to group II: ^ - P<0.001; ^^-- P<0.05

The maximum value of pro-inflammatory cytokine, IL-1β, was observed in patients with tympanic sclerosis against the background of cholesteatoma - 37.8±0.85 pg/ml, which was 1.4 times higher than the value of control group, (P<0.01) with the range of individual values from 30.2 to 42.2 pg/ml (Fig. 4.2).

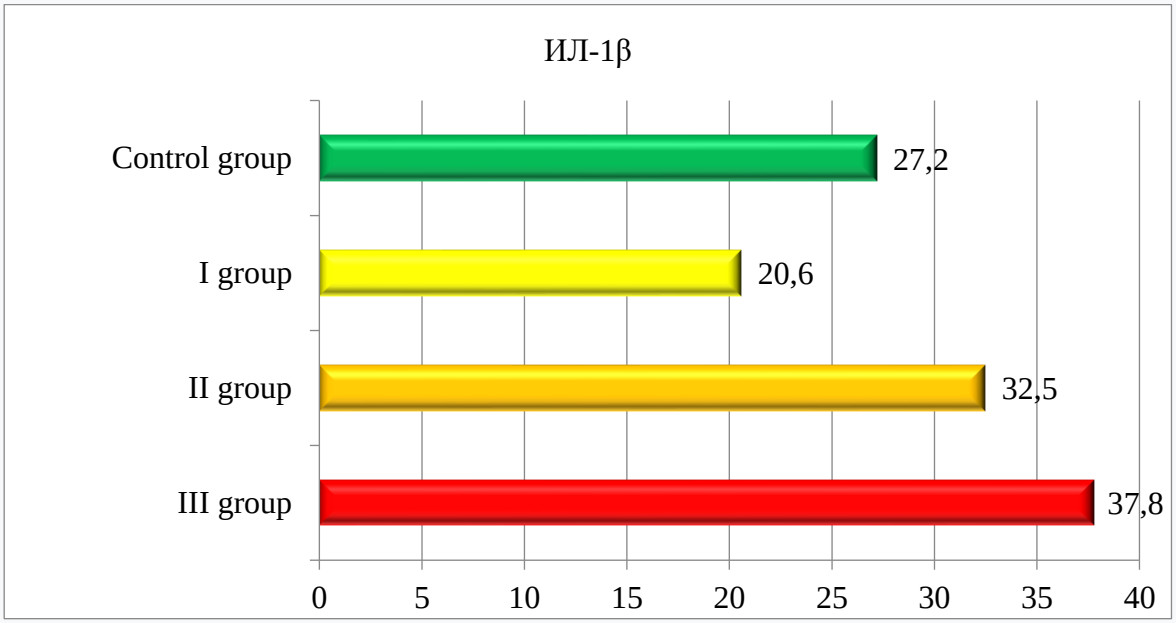

Fig.4.2. The level of IL-1β in patients with TSC depending on its forms, pg/ml

Thus, the true increase of IL-1β in systemic circulation at patients of study groups II and III was determined, which indicated the active inflammatory process in patients of that group.

The results analysis of study level for anti-inflammatory cytokine - IL-10 showed that in patients with limited form of tympanic sclerosis, the blood serum contains from 20 to 30.1 pg/ml, averaging 25.7 ± 0.91 pg/ml, which is 1.9 times higher than the values of control group ($P<0.001$). In patients with common form of TSC, the level of IL-10 in the blood serum averaged 19.3±0.75 pg/ml, which was 1.4 times higher than the values in the control group; the data were true significant relative to the control group ($P<0.001$) and relative to patients in group I ($P<0.001$). In patients with tympanic sclerosis with cholesteatoma, the level of IL-10 in systemic circulation averaged 21.4 ± 0.6 pg/ml, which was significantly higher than in control group ($P<0.001$), relative to the indices of group I ($P<0.001$) and relatively indices of group II ($P<0.05$) (Fig. 4.3).

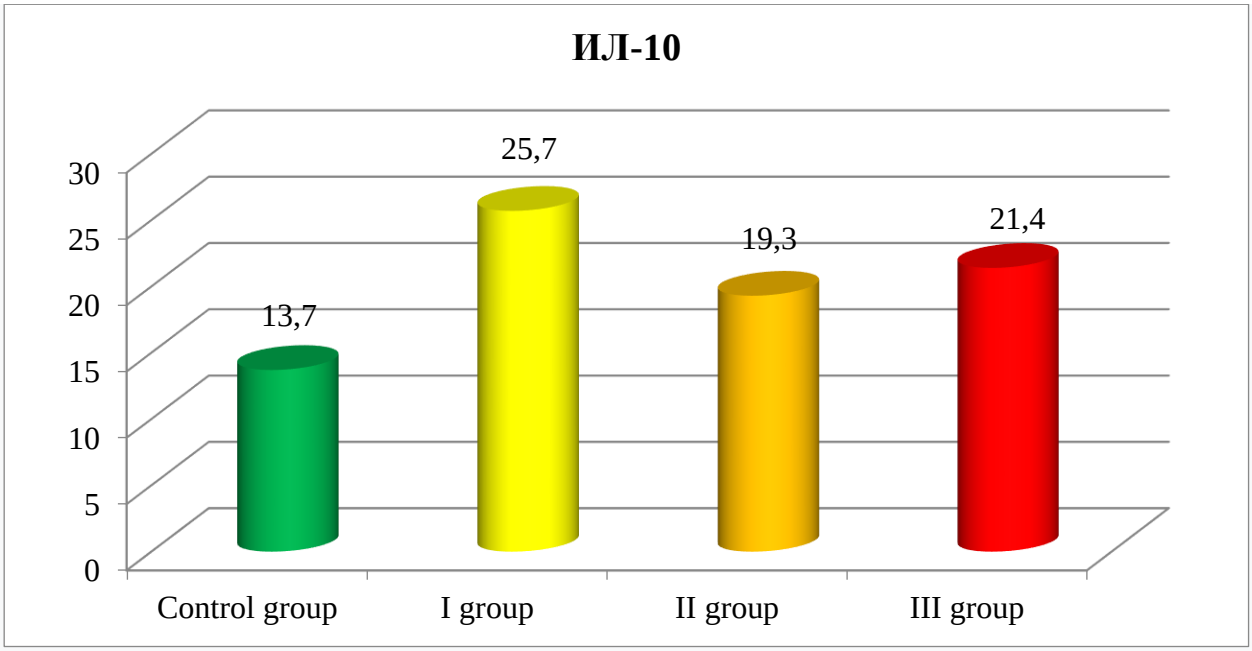

Fig.4.3. The level of IL-10 of patients with tympanic sclerosis pg/ml

As it can be seen from the data from Figure 4.4, the level of IFN-γ in limited form of tympanic sclerosis averaged 29.9±1.83 pg/ml was significantly higher than in control group (P<0.002). In patients with common form of tympanic sclerosis, the level of IFN-γ was 37.5 ± 0.91 pg/ml, that was significantly higher both relative to control group (P<0.001) and to the indices of group I patients (P<0.001), and the IFN-γ content in that group was maximum higher to other groups.

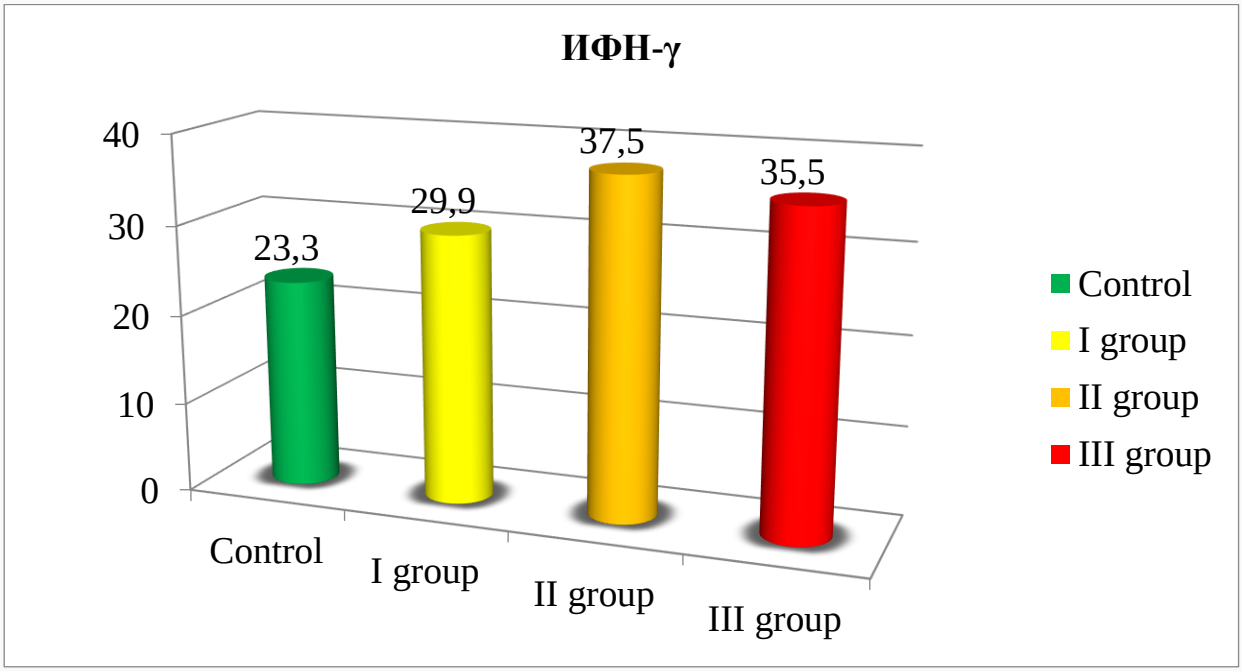

Fig.4.3. The level of IFN-γ in patients with tympanic sclerosis, pg/ml

The results analysis of study level for interferon-γ in patients with tympanic sclerosis against the background of cholesteatoma showed that this index in group was also increased and made up 35.5±1.02 pg/ml, which was significantly higher than indices in control group ($P<0.001$) and relative to the indices of patients in group I ($P<0.02$).

Thus, the results of studies conducted was to research the level of cytokines in
blood serum which showed that at limited tympanic sclerosis, the increased level
of IL-10 is noted. T he high production of this interleukin inhibits the production
of inflammatory IL-1β, which was observed in patients of that group.

In patients of groups II and III, on the contrary, the content of both IL-1β and IL-10 was increased, but IL-10 was significantly less relative to indices of group I patients. The increased content of interferon-γ the maintenance of auto-inflammatory mechanisms of immunity. On the basis of which it can be assumed the certain exhaustion of anti-inflammatory mechanisms of humoral immunity, which allows to make up the conclusion about manifestation of secondary immune deficiency, which is highly specific, and, it is largely determined by the type of tympanic sclerosis.

§4.2. Assessment of local cytokine status in patients with tympanic sclerosis

The response of immune system to chronic ear diseases is ambiguous. In some cases, the generalized immune response is observed, however, the local reaction is also of great importance. This is due to a number of reasons, and above all, to the well-known autonomy and isolation of hearing organ from other systems of the body. In connection with the above mentioned, there was carried out the study to determine the level of production for pro- (IL-1β and IFNγ) and anti-inflammatory (IL-10) cytokines in ear rinses.

As it can be seen from the data in Table 4.2, the level of IL-1β in the ear lavage of control group averaged 18.03±0.78 pg/ml. In patients with limited form of TSC the level of that cytokine within the control group was (18.8±0.43 pg/ml).

Table 4.2.

Level of cytokines in ear lavage in patients with tympanic sclerosis

Groups	IL-1β	IL-10	IFNγ
Control group	18,03 ± 0,78	5,3 ± 0,48	13,9 ± 0,43
I group	18,8 ± 0,43	24,02 ± 0,62*	8,8 ± 0,53*
II group	21,2 ± 0,44*#	21,9 ± 0,98*	9,1 ± 0,59*
III group	27,5 ± 0,4*#^	29,6 ± 0,8*#^	7,2 ± 0,39*##^^

Note: Values are significant relative to the control group data *P<0.001; **P<0.002; significant relative to group 1: # - P<0.001; ## - P<0.02; significant relative to group II: ^ - P<0.001; ^^-- P<0.01

And, in patients with common form of tympanic sclerosis, the level of IL-1β in the ear lavage averaged 21.2±0.44 pg/ml, which was significantly higher than control values (P<0.001) and relative to group I indices(P<0.001). At tympanic sclerosis with cholesteatoma, the level of IL-1β was averagely higher than both the control values - 27.5±0.26 pg/ml (P<0.001), and the average values of group I (P<0.001), and group II (P<0.001).

The increased level of IL-1β indicates the ongoing inflammatory process in the middle ear cavity in common form of TSC. The post-inflammatory sclerosis is the dynamic condition where hyperplastic, dystrophic, atrophic and necrobiotic processes occur.

Apparently, from the data presented, the level of anti-inflammatory cytokine – IL-10 in control group averaged 5.3 ± 0.48 pg/ml (Fig. 4.5). In patients with tympanic sclerosis, it was significantly increased, and the maximum value was observed at tympanic sclerosis in combination with cholesteatoma - 29.6±0.8 pg/ml, which was more than 5 times higher than the data in control group (P<0.001).

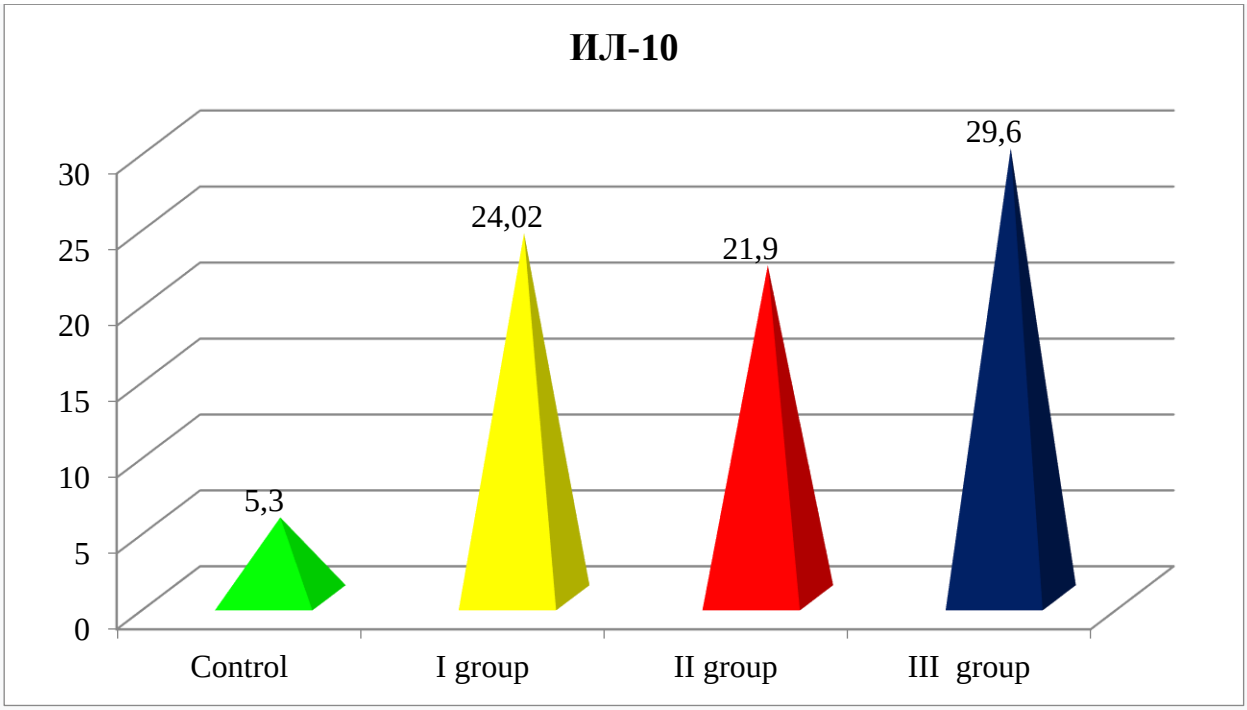

Fig.4.5. The local level of IL-10 in study groups, pg/ml.

However, in patients with the common form, the level of IL-10 was in 4.1 times higher than control values, averaging 21.9 ± 0.98 pg/ml (P<0.001) in 4 times. In patients with limited form of tympanic sclerosis, the level of IL-10 averaged 24.02 ± 0.62 pg/ml, which is in 4.5 times higher than the data in control group (P<0.001).

According to Serebrennikova S.N., Seminsky I.Zh., (2012), the excess of IL-10 leads to decrease in anti-infective protection and the development of chronic infections. Apparently, the systemic increase in secretion of IL-10 reduces the functional activity of cellular immune system, which can cause long-term pathological effects of pathogenic agents and contributes to persistence of bacteria [Sharkova V.A., Motavkina N.S.; Serebrennikova S.N., Seminsky I.Zh.].

The level of IFNγ in ear lavages of control group averaged 13.9±0.43 pg/ml. In patients with common form of tympanic sclerosis, the level of IFN-γ averaged 9.1 ± 0.59 pg/ml, which is in 1.53 times lower than the values of control group (P<0.001). the given index was considerably different with data of group I (P<0,001).

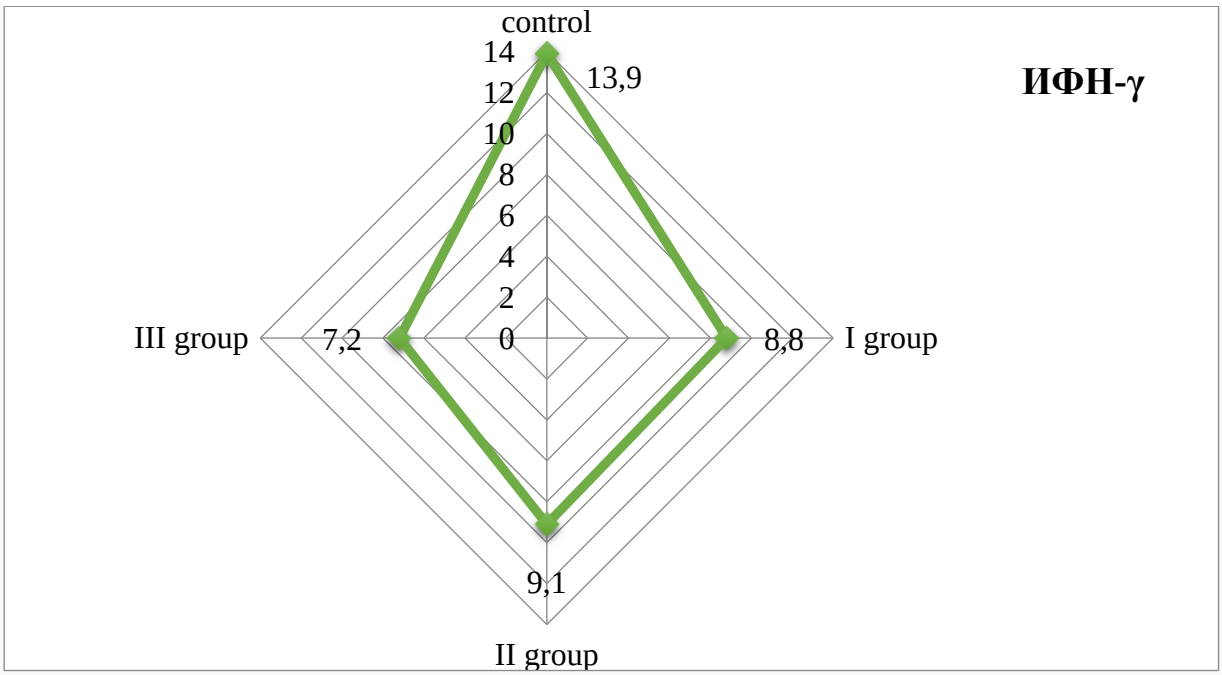

Fig.4.6. The local level of IFN-γ at study patients pg/ml.

In patients with limited form of TSC, the level of this interferon averaged 8.8±0.53 pg/ml, which was significantly lower compared with indices of control group (P<0.001), while, at the same time there were no significant differences between the indices of groups I and II, noted. The lowest synthesis of IFN-γ was observed in patients with combined form of tympanic sclerosis with cholesteatoma - 7.2±0.39 pg/ml, (P<0.001), also the values were considerably low in comparison with indices of group I (P<0.02) and group II (P<0.01). The reduced level of interferon-γ explains the undergoing of those patients the infections.

Evidently, it can be seen from presented data, in patients with tympanic sclerosis, the levels of pro-inflammatory cytokine IFN-γ and the anti-inflammatory cytokine IL-10 suffer profound changes. The imbalance in the ratio of IFN-γ and IL-10 has diagnostic and prognostic significance, that is, an increase in the severity of pathological process which leads to decrease in this ratio and indicates the development of deep defect in cell-mediated immune defense.

In this regard, there was considered that it is appropriate to calculate the index having combined those opposition indices and use the following formula: CI = (IFN-γ)/(IL-10); where CI is the cytokine index

The calculations showed that in practically healthy people (control group) CI was 3.02 conventional units.

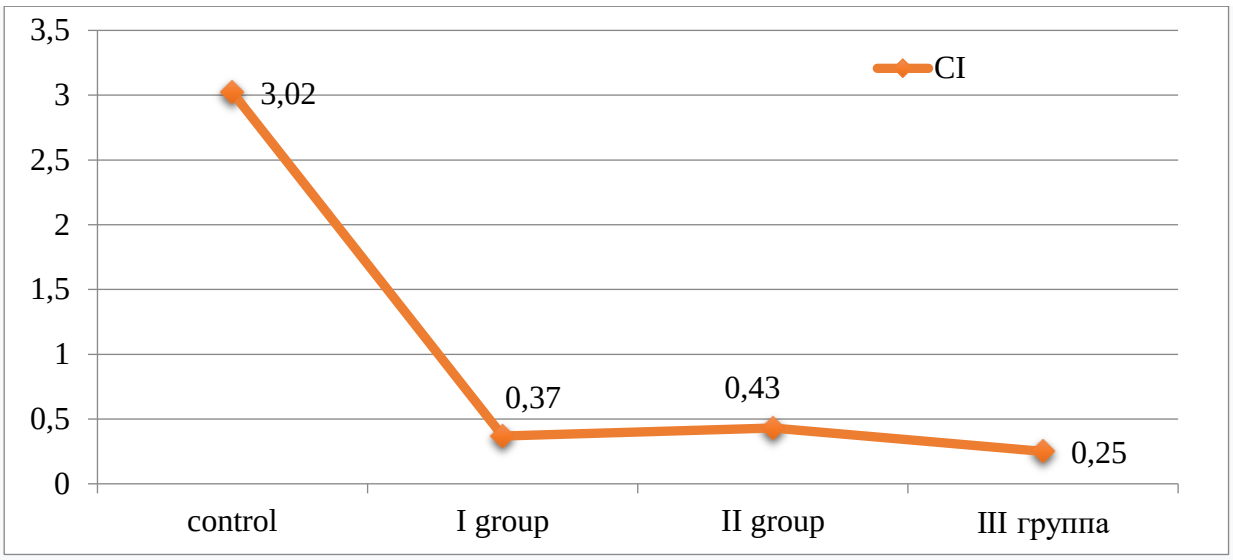

Fig.4.7. CI in patients of the study groups.

This index was sharply reduced in patients with tympanic sclerosis, and in the limited form it was 0.37 units, in the widespread form it was within 0.43 units, and when TSC was combined with cholesteatoma, this index was 0.25 units (Fig. 4.7.). Thus, the cytokine index of group I was significantly lower relatively to the control group (P<0.001) and to group III (P<0.001). In study group II the indices of cytokine were also significantly reduced relatively to the control group (P<0.001) and the differences were statistically insignificant with the indices of group I. In patients of group III, the cytokine index was significantly reduced accordingly to the control group (P<0.001), group I (P<0.001) and group II (P<0.001).

Therefore, when conducting studies to research the level of IFNγ and IL-10 in ear lavages and calculating CI, it is possible to predict what form of tympanic sclerosis is observed at patient. If 0.4< CI <1, then it is common form. If CI is from 0.4 to 0.3, it is limited form of TSC, and if <0.3, it is combination of TSC with cholesteatoma. The results obtained have the great importance at prescribing corrective measures.

Thus, the contribution of pro-inflammatory interleukins in maintaining chronic inflammation in TSC is undeniable. Symptoms characteristic of inflammatory process appear only if the pathogenic agent overcomes the supra-epithelial level of defense, which is represented by nonspecific mechanisms of immune system. At the same time, in order to

protect the underlying structures, the epithelial cells can cause local inflammation and attract a group of phage cells.

So, the activated macrophages produce cytokines, which, in their turn, promote the migration of monocytes, neutrophils, eosinophils and other cells to the focus of inflammation. The endothelium of damaged vessels change the properties of leukocytes and ensures their migration to the site of inflammation. Participation in the inflammatory process of interferon-gamma (IFN- γ) is determined by its biological effect. IFN-gamma activates the production of pro-inflammatory cytokines. This circumstance should be taken into account when determining treatment strategies and tactics. The method of choice in this system is complex anti-inflammatory and immune –corrective therapy.

Surgical treatment of patients with tympanic sclerosis

The most difficult task of surgical treatment of TSC is to determine the treatment tactics individually. The particular difficulties are caused by CPOM with TSC and TSC with cholesteatoma, since in these forms of the disease the surgeon will have to solve several problems – sanitation of tympanic cavity, mobilization the ossicular chain or install an implant, and, also, to perform plastic surgery of tympanic membrane or, as well as, to install an implant, while achieving the best functional outcomes.

When performing surgery on the middle ear in patients with CPMO and TSC, there were pursued two goals - sanitizing the cavity of eardrum and preventing the strengthening of sclerosis process, reconstructing the elements of sound-conducting system in order to preserve and improve hearing in patients. When choosing the volume of surgical intervention, the surgeons relied on prevalence and localization of sclerotic process, and degree of changes in structures of middle ear.

For the patients the operations were performed in in one or two stages, taking into account, the above mentioned criteria.

There were examined 66 patients diagnosed with CPMO and TSC. All patients underwent surgery (the course of operation is described in Chapter II).

Based on surgical approach, the patients were divided into 3 groups: group 1 included 18 patients, 4 of whom underwent endo-aural access through the ear funnel, the 2nd group consisted of 26 patients, 5 patients of whom underwent endo-meatal access, the remaining patients underwent tympanic plasty and other types of surgical interventions, which were performed through a post-auricular approach. The 3rd group consisted of 22 patients (combination of cholesteatoma with tympanic sclerosis) and all types of surgical interventions were performed through the post-auricular approach.

The patients were undergone several types of surgery: more than the half of patients had all kinds of tympanic plasty.

The tympanic plasty without use of prostheses was performed in 36 (54.5%) patients, 16 (24.2%) patients had partial and complete ossicular prostheses made of titanium (4; 6.1%) and Teflon (12; 18.2%). Other types of interventions were sanitizing surgery with closed tympanic plasty in 17 (25.7%) patients, revision of the tympanic cavity with ossicle plasty in 5 (7.57%) patients (7.57%), myringo-plasty in 5 (7.57%) patients and attico-anthrotomy with plastic surgery of the lateral wall of the attic in 1 (1.5%) patient.

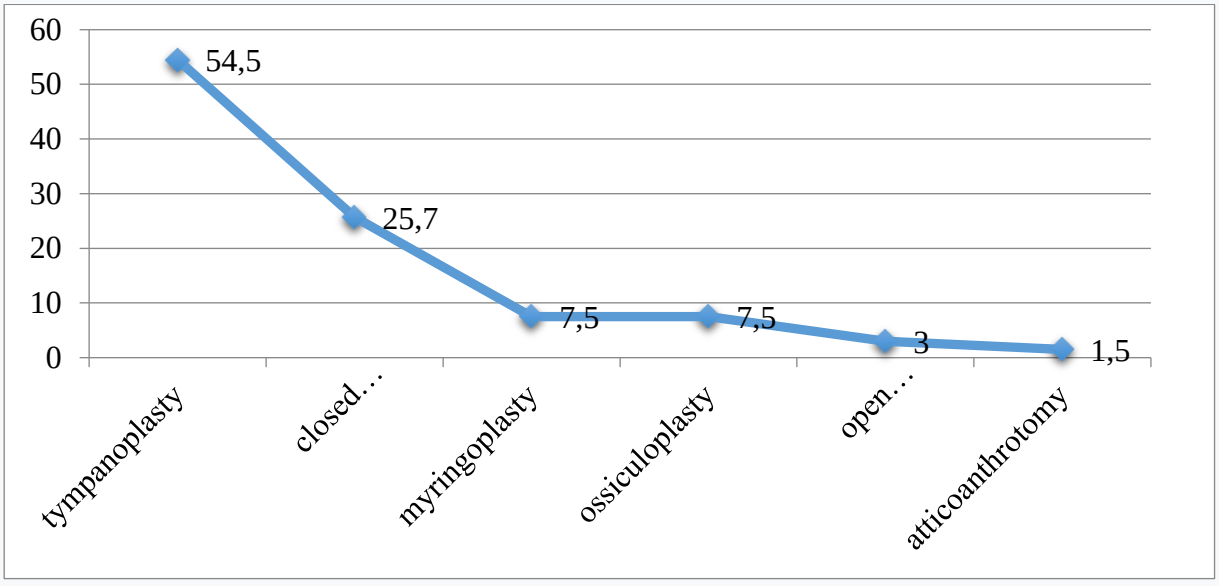

Fig. 4.8. The types of operations performed in patients with tympanic sclerosis (%).

If the result of surgical intervention was unsatisfactory - anatomical (3; 4.5%) or functional (5; 7.54%) - the repeat operation was performed,

during which the identified violations were eliminated. During reoperation, the remobilization of auditory ossicles (4; 6.06%) or correction of prosthesis position (3; 4.54%) was most often performed; in 1 (1.51%) patient the prosthesis was replaced with the longer one that was more suitable by type.

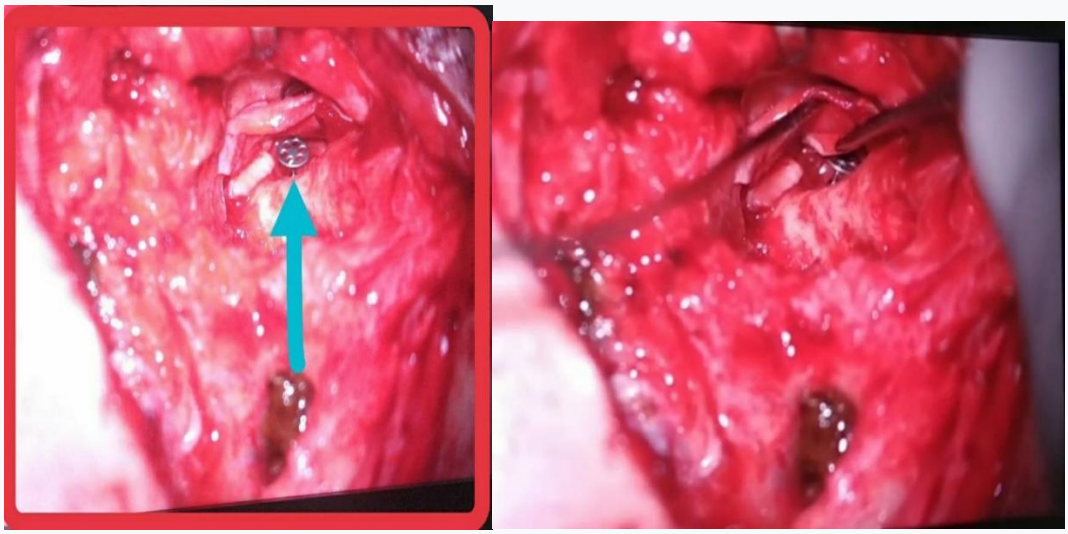

Fig.4.9. The tympanic plasty with one-stage installation of total stapes prosthesis.

Patient H.R. 22 years old with a right-sided widespread form of tympanic sclerosis 1- total prosthesis (titanium) 2- (a, c) to protect the prosthesis, cartilage obtained from the auricle was placed.

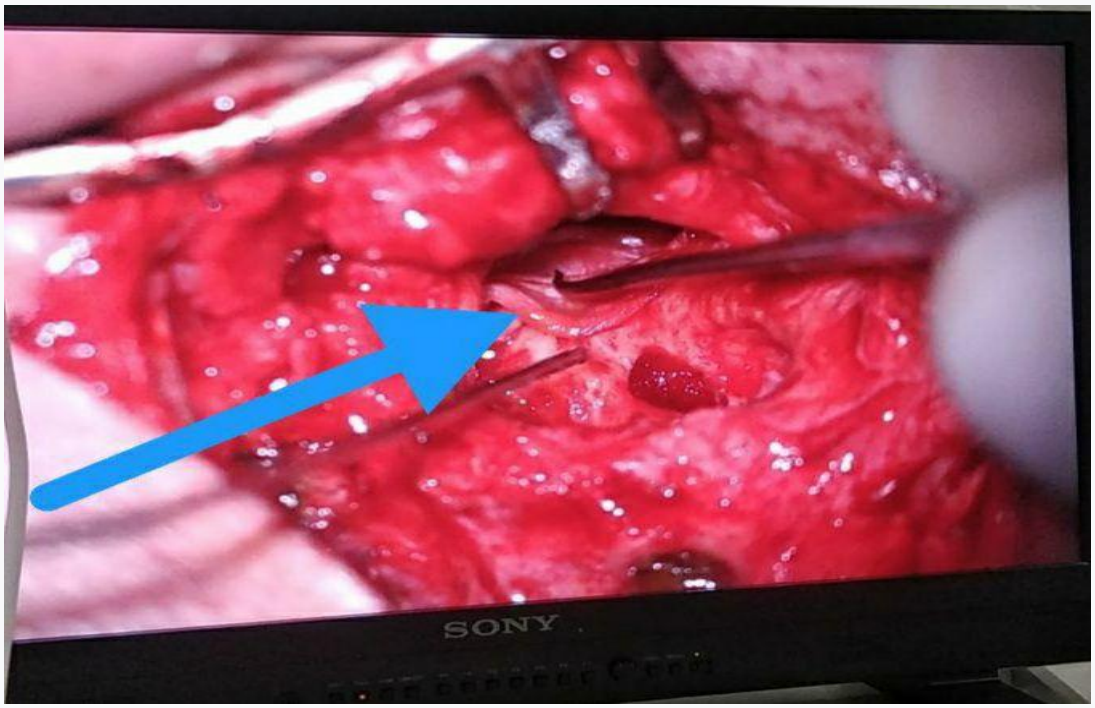

Fig.4.10. For tympanic plasty the temporalis muscle fascia (5-6 mm) was used and the tympanic membrane was created.

In postoperative period, the symptomatic therapy was carried out depending on health state, and, as well as the local therapy.

For a week, restorative and anti-inflammatory treatment was carried out, there were also the antibacterial, anti-inflammatory and analgesic drugs prescribed parenterally. The antibacterial therapy was prescribed for 5-7 days, the drugs of choice were cephalosporins - cefazolin or ceftriaxone at the dose of 1.0 g 2 times a day I/M or I/V. All patients were prescribed anti-edema and dehydration therapy in the first 3-5 days. Corticosteroids were used in short course lasting 3-5 days, usually prescribing dexamethasone at initial dose of 12 mg once a day I/M with a dose reduction according to the scheme 12 - 8 - 6 - 4 - mg. For anti-inflammatory purposes, they prescribed calcium gluconate 10%-10 ml + NaCl 0.9%-100 ml, intravenous drops were administered.

Pathogenetic approach to rehabilitation therapy for tympanic plasty

In order to prevent postoperative relapses of tympanic sclerosis during the rehabilitation period there was worked out the method of administering Longidaza using ultrasonic – phonophoresis.

The patient's position during ultrasonic procedure was lying on his side. The localization of effect was the peri-temporal region. The direct contact, medium contact was dry substance of drug "Longidaza" 3000 IU, t was diluted immediately before procedure in 5.0-7.0 g. medical mineral butter for ultrasonic exposure and applied on skin near the temporal region.

Fig. 4.9. The visual photo of drugs used during UT - Longidaza and Vaseline.

Fig.4.10. The ultrasonic therapy (own observation). Patient F., 53 years old after surgery.

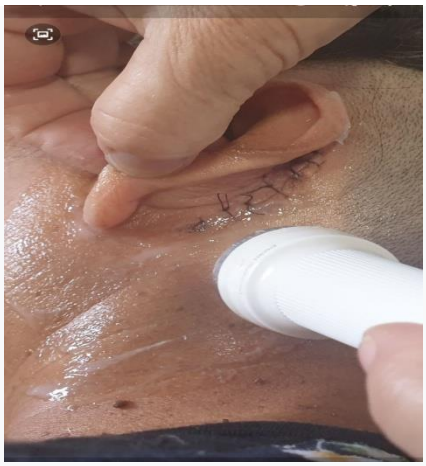

Fig. 4.11. The ultrasonic therapy (own observation). Patient A.Zh., 59 years old, with a common type of tympanic sclerosis. Tympanic plasty surgery was performing. Carrying out the UT procedure with Longidase on the 3rd day after surgery.

The patients with advanced form of SCT (n=26) received complex treatment using local UST therapy with the anti-fibrotic drug Longidase. The course dose of Longidase was 30,000 IU. The duration of therapeutic session was 15 minutes daily, once a day. The course of therapy includes 10 exposures. In all patients of the main group, the positive tolerability with the combination of Longidase 3000ME and Ultrasound were observed.

In the limited form (n=18), patients underwent the following measures: standard treatment was anti-inflammatory, antibacterial therapy, ear drops, physical therapy using the same method. The physiotherapeutic treatment was started after surgery on the 3rd day. After

each procedure, the operated ear was bandaged in the surgical dressing room, according to general accepted rules. When cholesteatoma was combined with tympanic sclerosis, the patients (n=22) were undergone the following corrective measures: they were: standard treatment - anti-inflammatory, antibacterial therapy, ear drops and dressings of operated ear.

The effectiveness and tolerability of complex treatment were assessed after 10 days of treatment. It should be noted that correct understanding of mechanisms underlying in the development of tympanic sclerosis allows to assess adequately the required volume of surgical and therapeutic care at each specific case and avoid possible mistakes.

The dynamics of following parameters (M±m) the level of cytokines (IL-1β, IL-10 and IFNγ) were researched. The results of taken studies in dynamics of pro- and anti-inflammatory cytokines as a result of treatment measures showed that there was not only the positive dynamics of clinical parameters, but also the levels of studied cytokines in the blood serum (Table 4.3).

Table 4.3.

Dynamics of studied cytokines in patients with tympanic sclerosis as a result of taken corrective measures

Indices pg/ml	Limited form of TSC n=18		Widespread form of TSC n=26		Choleastoma on background of TSC n = 22	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
IL-1β	20,6±0,9	25,9±0,8 *	32,5±0,6	28,3±0,7 *	37,8±0,9	30,6±1,5 *
IL-10	25,7±0,9	19,3±0,7 *	19,3±0,7 5	15,8±0,5 *	21,4±0,6	16,5±0,7 *
IFNγ	29,9±1,8	24,6±0,7 **	37,5±0,9	29,7±0,8 *	35,5±1,0 2	29,8±0,8 *

Note: values are significant in relation to data before treatment *-P<0.001; **-P<0.02

Thus, in patients with a limited form of TSC, in whom before treatment the level of IL-1β was significantly lower than control values, after the measures taken it increased, averaging 25.9±0.8 pg/ml (P<0.001).

(P<0,001).

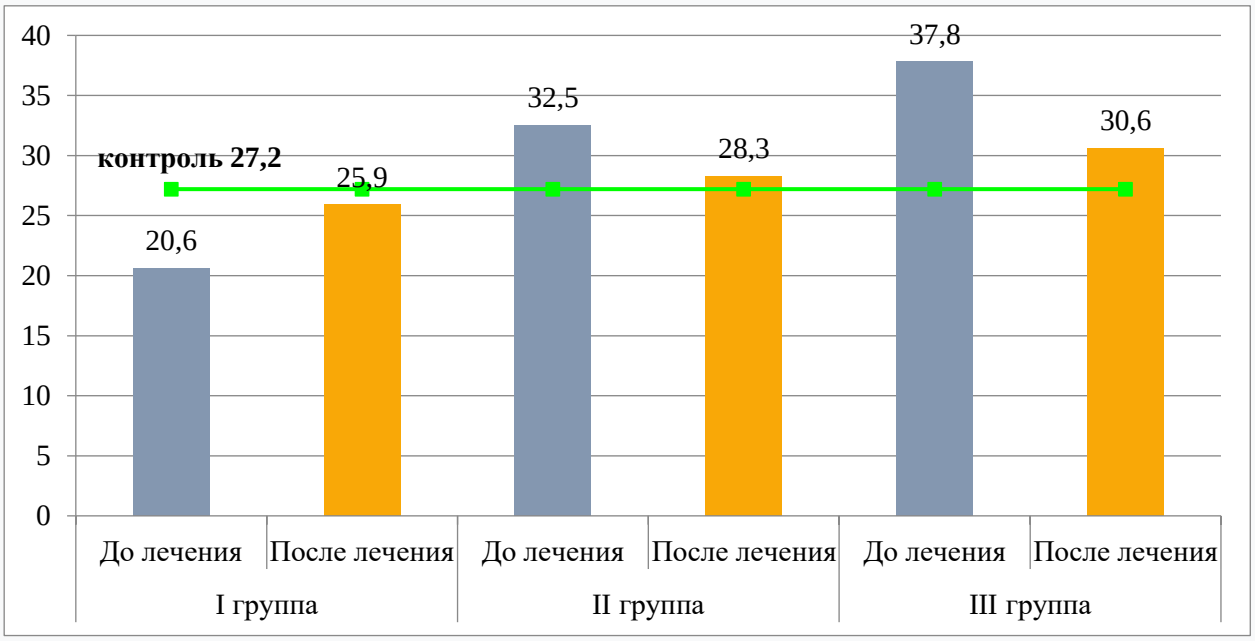

Fig.4.12. Dynamics of IL-1β levels in patients with tympanic sclerosis, pg/ml

The level of IL-1β in patients with the advanced form of TSC after treatment averaged 28.3±0.7 pg/ml, which was 1.2 times lower than the level before treatment (P<0.001). In patients with TSC with cholesteatoma, the level of IL-1β also significantly decreased, reaching an average of 30.6 ± 1.5 pg/ml, which was significantly lower relative to the initial values (P < 0.001).

The level of IL-10 after the treatment measures also showed positive dynamics. A significant decrease in that cytokine was observed in patients with a limited form of tympanic sclerosis, which averaged 19.3±0.7 pg/ml, which was significant relative initial values (P<0.001). In patients

with widespread tympanic sclerosis, the elevated level before treatment significantly decreased after treatment, averaging 15.8±0.5 pg/ml (P<0.001), (Fig. 4.13).

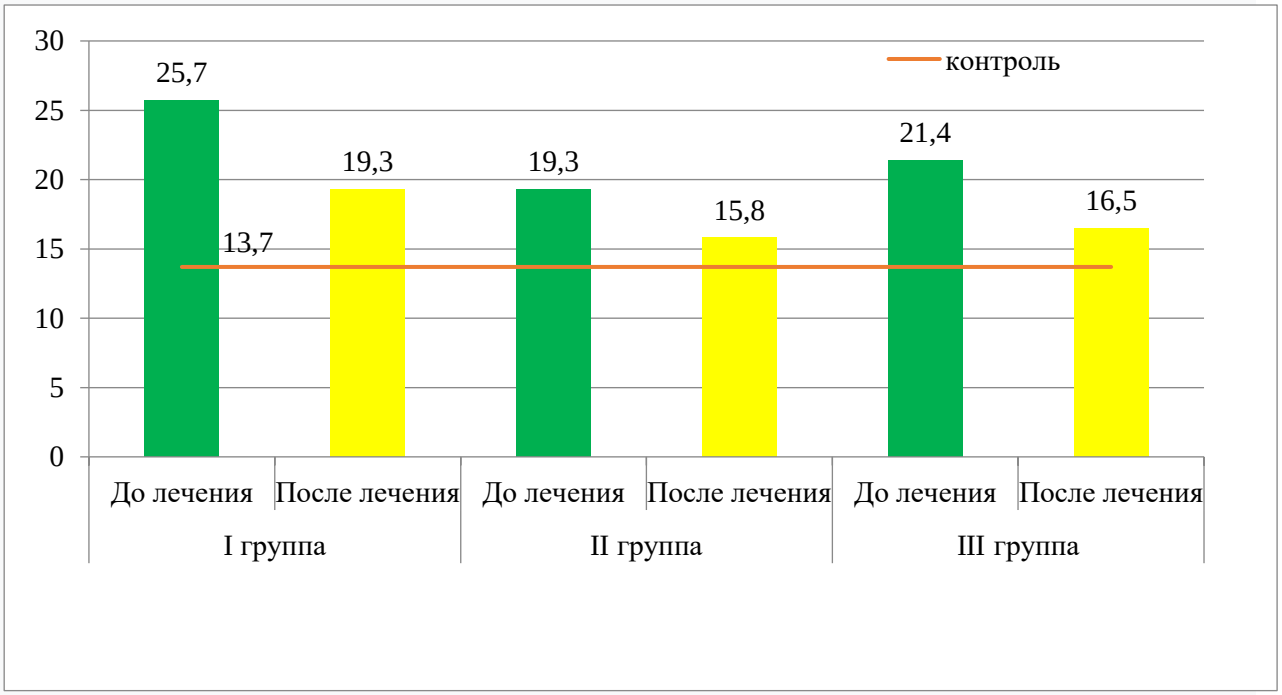

Fig.4.13. Dynamics of IL-10 as a result of taken treatment measures, pg/ml.

The changes in synthesis of IL-10 as a result of corrective measures also affected patients with tympanic sclerosis against the background of cholesteatoma. Thus, the increased level of IL-10 to 21.4±0.6 pg/ml, after treatment averaged 16.5±0.7 pg/ml (P<0.001).

IFN-γ is secreted by several immune cells, including macrophages, NK cells, and T cells play the role in directly stimulating major inflammatory effector cells. In our studies, the hypersecretion of interferon-γ was observed in tympanic sclerosis, and the maximum value was observed in patients with common form of tympanic sclerosis (Fig. 4.14).

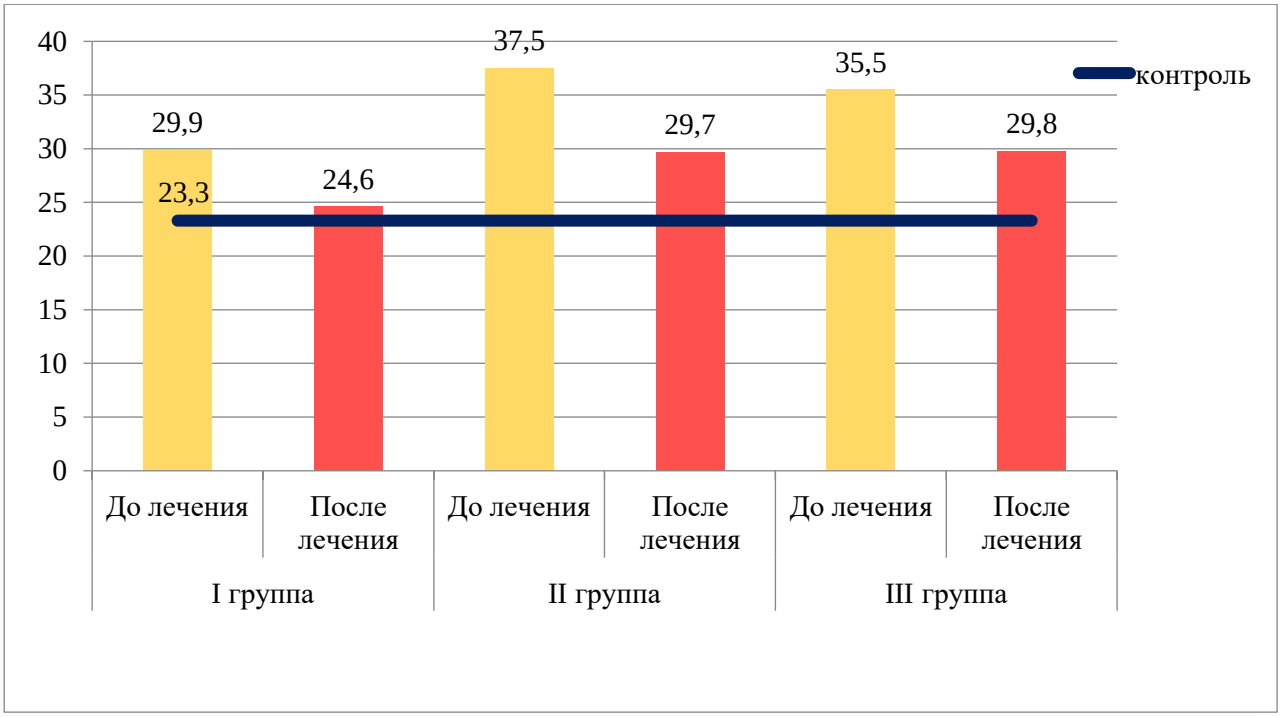

Fig.4.14. The dynamics of IFN-γ levels in patients with tympanic sclerosis as the result of treatment, pg/ml.

The patients with limited form of TSC had significant decrease in the level of IFN-γ to 24.6±0.7 pg/ml relative to the initial values (P<0.02). The patients with advanced form of TSC also had significant decrease in the level of IFN-γ to 29.7±0.8 pg/ml which was also noted as compared to the values before treatment (P<0.001). Also, a significant decrease in this interleukin was noted in group III of patients - to 29.8 ± 0.8 pg/ml, which was significantly significant compared to the values before treatment (P < 0.001).

Thus, the taken corrective measures contributed not only to positive dynamics of clinical parameters, but also contributed to the positive dynamics of level for both pro- and anti-inflammatory cytokines. The assessment of cytokine index, the ratio of anti-inflammatory and pro-inflammatory cytokines showed the decrease in their dynamics (Fig. 4.15).

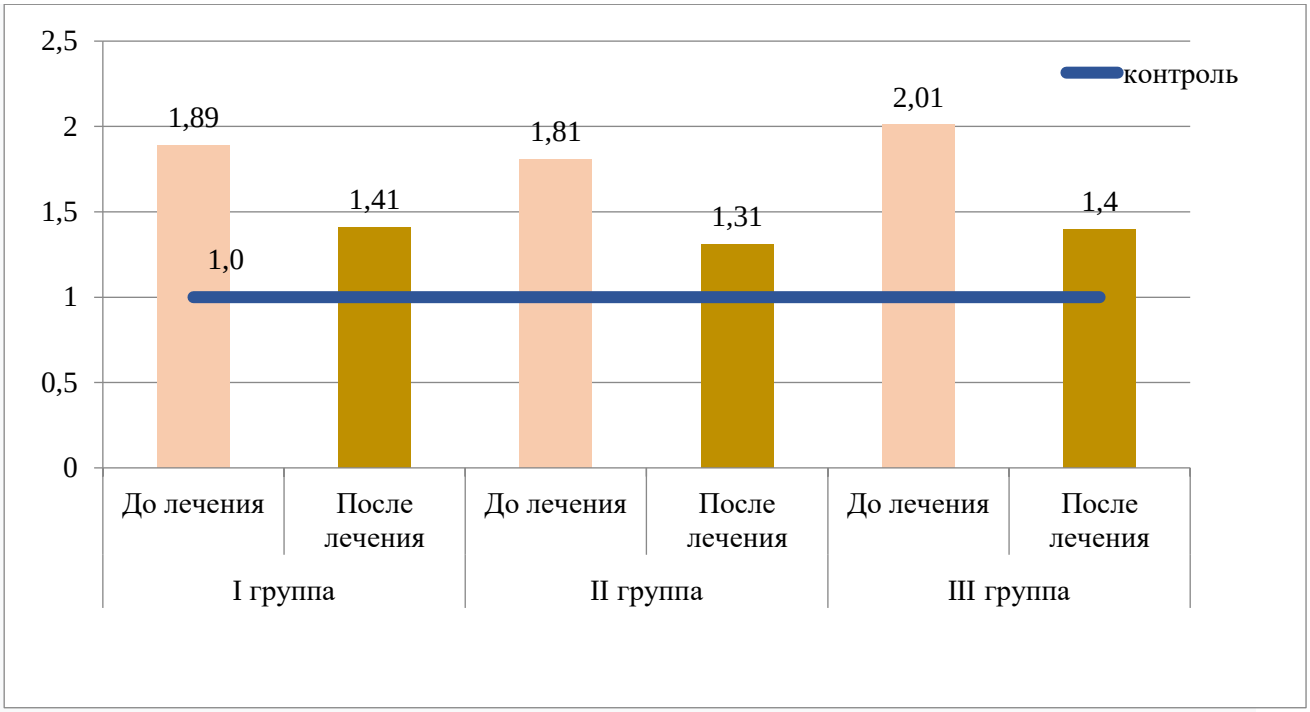

Fig.4.15. The dynamics of cytokine index in patients of study groups.

Besides, the effectiveness and tolerability of complex treatment were assessed by the dynamics of the following clinical indices: reduction of pain, post-operative cessation of exudation from the surgical area, decrease of hyperemia in surgical area, and reduction of local edema.

The additional use of USI + Longidase made it possible to significantly increase the number of patients assessing their life quality as "good" or "excellent". The patients' examinations were carried out at admission to the hospital and after completion of physiotherapy course. On the background of treatment with Longidase, more pronounced positive changes in health-related life quality indices were noted: in the majority of patients, the psychological health improved.

Table 4.5

The dynamics of clinical parameters after treatment patients of study groups

Indices		Main group (n=26)	Control group (n=22)	Comparison group (n= 18)
Pain reduction at operating area in 2-3 days		24 (92,3%)	10 (45,5%)*	14 (77,78%)***^
Postoperative cessation of exudation from the surgical area for 30 days, on 33 -35 days		22 (84,6%) 4 (15,4%)	11 (50%)** 11 (50%)**	12 (66,66%) 6 (33,33%)
Reduction of hyperemia in the surgical area on 7 day		20 (76,9%)	13 (59,09%)	12 (66,67%)
Reducing swelling, on 4-5 days on 7-8 days		20 (76,9%) 6 (23,1%)	9 (40,91%)** 13 (59,1%)**	12 (66,67%) 6 (33,3%)
Reduction of weakness after surgical interventions on 7 day		21 (80,8%)	13 (59,1%)	13 (72,22%)
Life quality is:	satisfactory	-	6 (27,3%)**	1 (5,56%)
	good	8 (30,8%)	13 (59,1%)***	13 (77,8%)**
	excellent	18 (69,2%)	3 (13,6%)*	3 (16,67%)*
Removal stitches after surgery, on 6-7 days on 8-9 days		24 (92,3%) 2 (7,7%)	9 (40,9%)* 13 (59,1%)*	11 (61,1%)** 7 (38,9%)**

Note: *-P<0.001, **-P<0.02; ***-P<0.05 – the difference is significant relative to the main group, ^-P<0.05 – the difference is significant relative to the control group.

The effectiveness and tolerability of complex treatment were assessed after 6-12 months by the dynamics of the following indices: relapse of TST, effectiveness of therapy, and the frequency of inflammatory diseases for upper respiratory tract over the past year.

Table 4.6.

The effectiveness of therapy after 12 months of surgery

Indices	**Main group (n=26)**	**Control group (n=22)**	**Comparison groupIndex (n= 18)**
Indices of upper respiratory tract diseases: influenza, ARVI within 1 year.	5 (19,23%)	11 (50%)*	5 (27,8%)
Relapse of TSC	1 (3,8%)	5 (22,7%)	2 (11,1%)
Efficiency	96,15%	77,3%	88,89%

Note: *-P<0.05 difference is significant relative to the main group

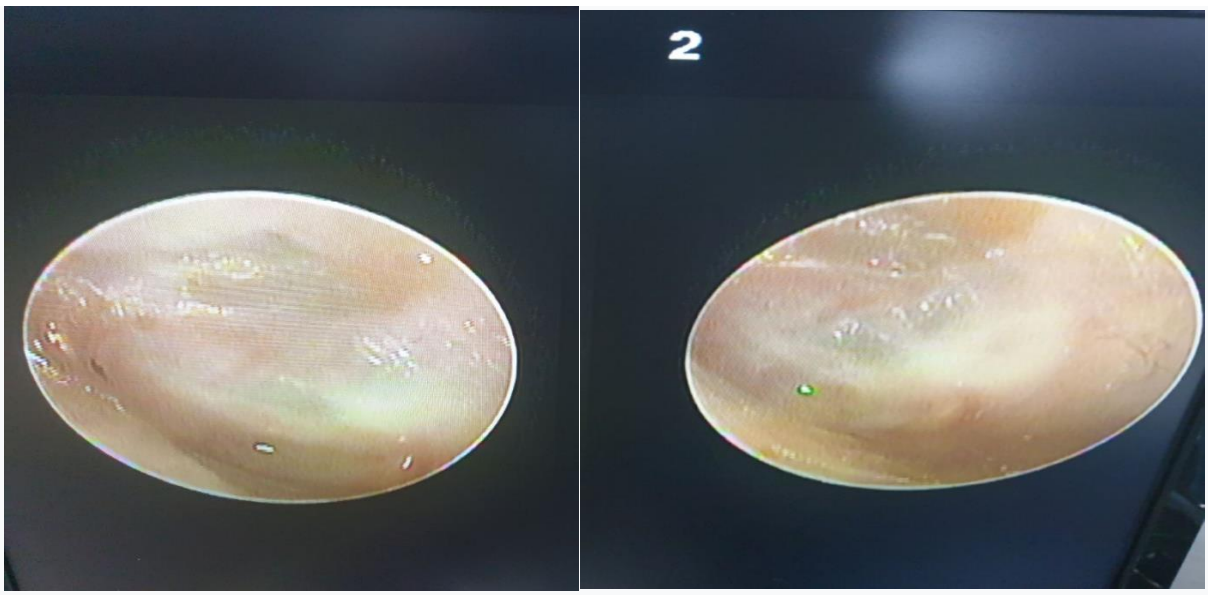

Fig. 4.17. 1) Patient I.R. 34 years old. (own observation) After tympanic plasty, 12 months later, oto-microscopic view (AS)
2)Patient L.Sh. 46 years old. (own observation) After tympanic plasty, 18 months later, oto-microscopic view (AD)

The content of IL-1β, which was 32.5±0.6 pg/ml at admission in the main group of patients, decreased to 28.3±0.7 pg/ml after Longidaza + UST, i.e. 1.2 times ($p<0.001$). Its action contributed to decrease of IL-1β content to the level of that in healthy people. The positive aspect of using Longidase in combination with basic therapy was a decrease of body's sensitiveness to viral and bacterial agents, which was noted by almost all patients, receiving Longidaza. This leads to decrease in diseases incidence of upper respiratory tract, sinusitis, eustachitis, chronic otitis, and, ,also, it reduces the development of various inflammatory processes in middle ear, relapses of disease and number of complications. Taking into account the modern understanding of pathogenesis and patho-morphology of tympanic sclerosis, it is advisable to use UST with Longidase only in treatment of this disease, but also for the purpose of preventing sclerotic changes in the middle ear and tympanic cavity and after surgery.

Longidase increases the bioavailability of drugs, prolongs the action of hyaluronidase, and also suppresses inflammatory reactions, reduces

stimulating development of fibrotic process, which makes it possible to use it for the prevention and correction of fibrosing and sclerosing, dystrophic changes in the cavity of eardrum. For the same reason, Longidaza reduces the risk of relapses and re-fixation of stapes, that significantly reduces the frequency of hospitalization due to relapses of T SC.

At dynamics in 12 months after surgical and rehabilitation therapy, TPA data were also assessed (Table 4.7.).

Table 4.7.

Data of TPA in study groups before and after treatment

Forms of hearing loss	**I group**		**II group**		**III group**	
	before treatment	**after treatment**	**before treatment**	**after treatment**	**before treatment**	**after treatment**
Conductive	34,3±1,04	21,8±0,7*	-	-	-	
Mixed	43,56±4,5	25,9±1,7*	57,8±2,3	24,9±1,8*	59,3±3,8	32,5±2,7*^#
Sensorineural	-	-	-	-	29,0	26,0

Note: the difference in means is significant relative to before treatment *-P<0.001; relative to after treatment in group I ^-P<0.05; relative to after treatment of group II #-P<0.05.

According to the TPA data, patients of all groups had significantly improved hearing relative to the initial values (P < 0.001); the more pronounced improvement in hearing was observed in patients of groups II and III.

Thus, in patients of group I with conductive hearing loss, initially this index was 34.3 ± 1.04 dB, then after treatment it was 21.8 ± 0.7 dB (P <

0.001), in patients with mixed hearing loss before treatment the TPA indices were 43, 56±4.5dB, after treatment 25.9±1.7dB (P<0.001).

In patients with common form of TSC, only a mixed form of hearing loss was noted, and initial data were 57.8 ± 2.3 dB, and after treatment 24.9 ± 1.8 dB (P < 0.001).

In patients after treatment, the indices were also improved, but slightly less level in comparison with groups I and II. So, if before treatment the TPA indices were 59.3±3.8 dB, then after treatment they were 32.5±2.7 dB (P<0.001). The indices after treatment also remained relatively high in comparison with group I (P<0.05) and group II (P<0.05).

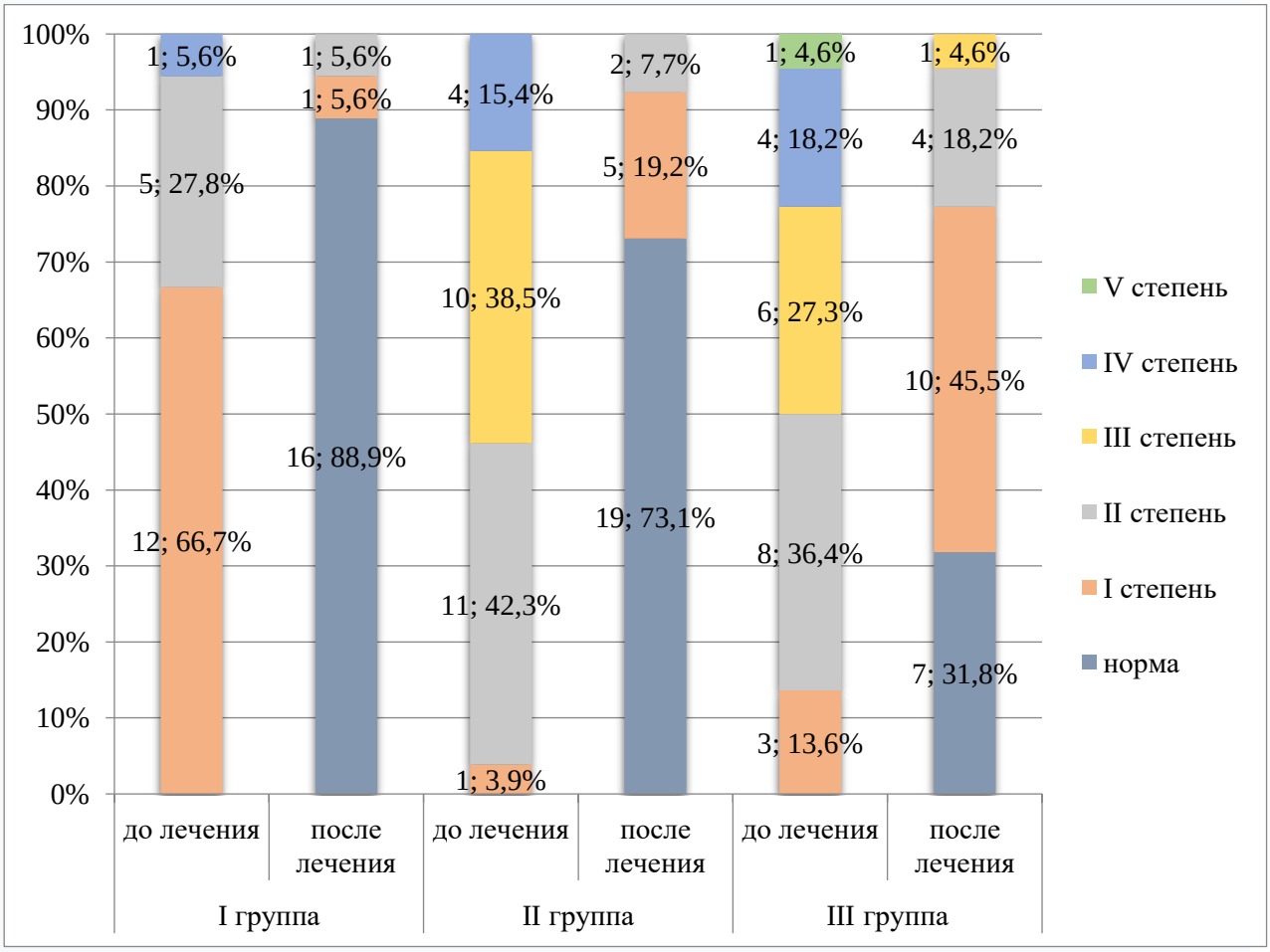

Fig.4.16. The distribution of patients depending on degree of hearing damage before and after treatment.

After taken therapy, the significant improvement in level of hearing impairment was noted. Thus, in patients of all study groups before

therapy, the normal values of TPA were not noted, but after therapy in patients of group I, normal values were already noted in 16 (88.9%) patients, in group II - in 19 (73.1%) patients, and in group III group 7 (31.8%)patients (P<0.001). After rehabilitation therapy of grade IV, the study groups were no longer identified, and only in group III patients were observed III level of hearing loss. It should be noted that the data before and after treatment were true significant (P<0.05).

Conclusions to Chapter 4

According to the results of studies, the level of pro-inflammatory IL-1β in the blood serum was significantly higher (P<0.001) relative to the control level in patients with widespread TSC and tympanic sclerosis with cholesteatoma, which prove the active inflammatory process, and, as well as the level of IL-1β was reduced in the group of patients with limited tympanic sclerosis (P<0.001), indicating some depletion of immune responses. The content of IL-1β was also increased in the ear lavages of patients with advanced TSC (P<0.001) and TSC with cholesteatoma (P<0.001), and within the reference values in the group of patients with limited tympanic sclerosis.

The level of anti-inflammatory IL-10 in the blood serum was significantly (P<0.001) increased relative to control group in all patients with tympanic sclerosis, and in patients with the common form of TSC (P<0.001) and tympanic sclerosis with cholesteatoma (P<0.001) the level of IL-10 was significantly lower according to the group with limited form of tympanic sclerosis, which proves some depletion of anti-inflammatory in the immune system. In ear swabs, the content of IL-10 was significantly increased in all study groups (P<0.001).

The level of IFN-γ in the systemic circulation showed a significant increase relative to the control both in the group of patients with tympanosclerosis against the background of cholesteatoma and widespread tympanosclerosis (P<0.001), and in patients with limited tympanosclerosis (P<0.001). At the same time, in ear lavages, the level of IFN-γ was significantly reduced in all study groups (P<0.001).

At the result of rehabilitation therapy, the level of IL-1β, IL-10, IFN-γ in the serum was approached to normal values in patients using the drug Longidaza ($P<0.001$), while in patients with traditional therapy there were statistically significant differences in the average values of the content IL-1β not determined.

As a result of rehabilitation therapy, the hearing improved according to TPA data in all study groups ($P<0.001$).

The use of Longidase against the background of standard therapy significantly promotes the disappearance or reduction of symptoms of disease ($P<0.005$), regression of inflammatory-proliferative changes in the middle ear, tympanic cavity ($P<0.001$) and reduces the frequency of relapses ($P<0.05$).

CONCLUSION

Hearing loss and deafness are a serious social problem, as they often cause disability in patients of working age, contribute to the social stigmatization of patients, and thereby worsen the patient's quality of life.

One of the causes of hearing loss is often tympanosclerosis, which develops as a complication of recurrent acute otitis media,
secretory otitis and chronic otitis. According to various authors, the prevalence of TSC against the background of CSR ranges from 3.3 to 33%, on the basis of which we can conclude that this disease is not entirely rare. The development of timely and pathogenetically substantiated methods of therapy will improve hearing in patients with TSC, prevent severe degrees of hearing loss in patients, and also avoid relapses in the postoperative period, which determines the relevance of this study.

The studies were carried out at the clinic OOO "Happy life" medical center LLC, TashPMI and at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, for the period 2019 - 2021. A clinical study was conducted on 66 patients with tympanic sclerosis aged from 18 to 69 years. It should be noted that the number of female patients prevailed, the proportion of which was 45 (68.18%) patients. All patients were concerned about hearing loss at the time of treatment. The sample was divided into 3 groups. Group I – 18 (27.3%) patients with limited tympanic sclerosis, in whom tympanic sclerotic plaques were located in one area - on the eardrum, on the walls of the tympanic cavity or on one of the auditory ossicles. Among them, there were 7 (38.9%) male and 11 (61.1%) female patients. The average age was 27.83±2.24 years (Me-27 years; min-18; max-54).

Group II – 26 (39.4%) patients with widespread tympanic sclerosis, involving the entire chain of auditory ossicles, the area of the oval or round window, tympanic cavity, cave or attic. Among this group there were 8 (30.8%) men and 18 (69.2%) patients. The average age was 33.35±2.6 years (Me-32 years; min-18; max-62).

Group III – 22 (33.3%) patients with a mixed form of tympanic sclerosis with cholesteatoma, in whom oto-microscopy revealed tympanic sclerotic calcified plaques in parallel with granulations, with desquamated epidermis, mucositis and cholesteatoma. The average age was 33.35±2.6 years (Me-35.1 years; min-18; max-69).

The main peak of incidence occurred in the age group of 18-40 years - 77.3% of the total number of subjects, that is, they belonged to the group of young and middle-aged people, as well as women of reproductive age, which is of great medical and social importance.

The sample was formed as a result of a survey of 437 patients with CSR. When compiling study groups, inclusion and exclusion criteria were taken into account. The examined patients underwent clinical, instrumental, immunological research before and after the proposed treatment methods. The anamnesis was studied to determine risk factors for the development of SCT in patients with CSR. In the development of TSC, significant and reliable risk factors were diseases of the thyroid gland ($P<0.001$), and chronic diseases of the digestive system ($P<0.005$), diseases of the lower respiratory tract ($P<0.001$,diseases of the cardiovascular system ($P<0.001$), chronic inflammatory diseases of the urinary system ($P<0.001$).Also significant in the development of TSC were frequent ARI (3-4 times a year), complicated by AOM, sinusitis

(P<0.001), deviated nasal septum (P<0.001), chronic sinusitis (P<0.001), duration of CSO (P<0.001), as well as the patient's gender (P<0.001) – female.

The prevailing, and often the only complaint in patients with tympanic sclerosis with or without fixation of the auditory ossicles, was a complaint of hearing loss n=66 (100%). Clinical symptoms were more severe and more pronounced in patients of groups II and III. Thus, periodic tinnitus was recorded significantly in a larger number of patients in group II (P<0.02). In 14 (77.8%) patients of group I, discharge from the ear was mucopurulent in nature, which was significantly more than the number of patients II (P<0.02) and III (P<0.001 groups. We did not detect purulent discharge in patients of group I, while in patients of group II (P<0.001) and group III (P<0.001), it significantly prevailed. The foul odor of the discharge was statistically significantly higher in patients of group III relative to patients of group I (P<0.001) and group II (P<0.001). There were significantly more patients experiencing pain in the mastoid area among patients' group III (P<0.005). Also, there were significantly more patients experiencing ear pain and headache in group III compared to patients in group I, P<0.02 and P<0.01, respectively. With a long course of the pathological process (more than 5 years), along with progressive hearing loss, symptoms such as noise in ear, rumble, poor speech intelligibility, facial asymmetry, etc. are observed. These symptoms dominated in the group of patients with TSC and cholesteatoma. The oto-microscopic examination data showed the presence of central perforation of tympanic membrane in 27 (40.9%) patients, subtotal perforation in 16 (24.2%) patients, total perforation in 15 (22.8%)

patients, and no perforation of the tympanic membrane was observed in 8 (12.1%) patients. During intervention the results of oto-microscopy revealed polymorphism of changes in the tympanic membrane and tympanic cavity - in some patients behind the tympanic membrane was found whitish, oval, spherical, bean-shaped, and even resembling pearls TSC plaques of various sizes. TSC pearl-like plaques were more often found in the group with the common form of TSC. For determination of degree for hearing loss the tone threshold audiometry was performed. According to results data of tone threshold audiometry having performed for all patients in the study groups, there were revealed the mixed form of hearing loss in 56 (84.8%) patients, the conductive form in 9 (13.6%) patients, and sensorineural form only in 1 (1.5%) patient.

The presence of only the conductive component of hearing loss in patients can be explained by location of TSC plaques - they were located only on tympanic membrane, without involving the osseous chain, perforations of the tympanic membrane were small in size, TSC plaques, the consistency of which was not solid and cartilaginous and covered only limited areas of tympanic cavity . The disease duration of those patients were no more than 2 years. The degree of hearing loss in patients with TSC varied from grades I to IV level. 1 degree of hearing loss was detected in 16 (24.2%) patients, moreover, the degree of hearing loss was statistically significantly more prevailed in group I patients relative to patients in groups II ($P<0.001$) and III ($P<0.005$). The more severe degrees of hearing loss (grades II-IV) were significantly more often observed in patients with widespread TSC and TSC with cholesteatoma relative to limited TSC ($P<0.05$). The tonal hearing threshold in patients

of group II (57.8±2.26dB) and group III (57.89±3.87dB) was significantly higher relative to group I (38.9±2.6dB), the difference was statistically significant (P <0.001 and P<0.001, accordingly).

To determine the state of local and general immunological status, the study of peripheral blood and ear lavage was carried out in order to study the content of IL-1β, IL-10 and IFN-γ.

In patients with limited form of tympanic sclerosis the level of IL-1β was 1.3 times lower than the values in control group and averaged 20.59±0.94 pg/ml (P<0.001). The induction of IL-1β synthesis in patients with a limited form of tympanic sclerosis reflects the characteristics of inflammatory process, that is, the chronicity of the inflammatory process. The level of IL-1β in patients with common form of tympanic sclerosis was 1.2 times higher than the control data and TSC with cholesteatoma and 1.4 times higher than the value in control group (P<0.01), which indicates the active inflammatory process in patients with this type groups.

The analysis of results for study of anti-inflammatory cytokine - IL-10 showed that in patients with limited form of tympanic sclerosis, the results were higher than the values of control group (P<0.001), as well as in the group of patients with a widespread form of TSC (P<0.001) and in patients with tympanic sclerosis with cholesteatoma (P<0.001).

The level of IFN-γ relative to the control group was higher in all study groups - limited form of TSC (P<0.002), widespread form of TSC (P<0.001) and TSC with cholesteatoma (P<0.001). High production of IL-10 inhibits the production of inflammatory IL-1β, which was observed in patients with a limited form of T SC. In patients of groups II and III, on

the contrary, the content of both IL-1β and IL-10 was increased, but IL-10 was significantly less than indices of patients in group I. But the increased level of interferon-γ indicates the maintenance of auto-inflammatory mechanisms of immunity. On the basis of that it can be assumed some depletion of anti-inflammatory mechanisms of humoral immunity, which allowed to conclude on manifestation of secondary immune deficiency, which was very specific and largely determined by the type of tympanic sclerosis. In some cases, the generalized immune response was observed, however, the local reaction was also of great importance. It was caused by the number of factors and, above all, the well-known autonomy and isolation of the hearing organ from other body systems.

In connection with the above, the study was carried to determine the level of production of pro- (IL-1β and IFNγ) and anti-inflammatory (IL-10) cytokines in ear swabs. In patients with limited form of TSC, the level of IL-1β was within the control group values - 18.8±0.43 pg/ml. In patients with common form of tympanic sclerosis, the level of IL-1β in the ear lavage was significantly higher than the control values ($P<0.001$) and relative to the indices of group I ($P<0.001$). In tympanic sclerosis with cholesteatoma, the level of IL-1β averagely was also significantly higher both in control and average values of group 1($P<0.001$) and groupII ($P<0.001$).

An increased level of IL-1β indicated the ongoing inflammatory process in the middle ear cavity at the common form of TSC. The post-inflammatory sclerosis is was a dynamic condition where hyperplastic, dystrophic, atrophic and necrobiotic processes occur.

In patients with tympanic sclerosis, the level of IL-10 was significantly increased, and the maximum value was observed at tympanic sclerosis with cholesteatoma, which was in 5 times higher than the data in the control group ($P<0.001$). In patients with the common form, the level of IL-10 was higher than control values in 4.1 times ($P<0.001$), in patients with a limited form of tympanic sclerosis it was 4.5 times higher than the data of control group ($P<0.001$).

According to Serebrennikova S.N., Seminsky I.Zh., (2012), excess IL-10 leads to a decrease in anti-infective protection and the development of chronic infections. Apparently, a systemic increase in the secretion of IL-10 reduces the functional activity of the cellular immune system, which can cause long-term pathological effects of pathogenic agents and contributes to the persistence of bacteria [Sharkova V.A., Motavkina N.S.; Serebrennikova S.N., Seminsky I.Zh.].

In patients with a widespread form of SCT, the level of IFN-γ is 1.53 times lower than the values of the control group ($P<0.001$), this index was significantly different from the data of group I ($P<0.001$). In patients with limited form of TSC, the level of IFN-γ was significantly lower compared to the indices of control group ($P<0.001$), at the same time, no significant differences were noted between the indices of groups I and II. The lowest synthesis of IFN-γ was observed in patients with combined form of tympanic sclerosis with cholesteatoma ($P<0.001$), and the values were also significantly low compared to indices of group I ($P<0.02$) and group II ($P<0.01$). The reduced level of interferon-γ explain the susceptibility of these patients to infections. Thus, the contribution of pro-inflammatory interleukins in maintaining chronic inflammation in TSC is undeniable.

Symptoms characteristic of inflammatory process appear only if the pathogenic agent overcomes the supra-epithelial level of protection, which is represented by nonspecific mechanisms of immune system. In this case, in order to protect the underlying structures, the epithelial cells can cause local inflammation and attract a group of phage cells. Thus, the activated macrophages produce cytokines, which, in their turn, promote the migration of monocytes, neutrophils, eosinophils and other cells to the focus of inflammation. The endothelium of damaged vessels, in its turn, changes the properties of leukocytes and ensures their migration to the site of inflammation. The participation of interferon-gamma (IFN-γ) in the inflammatory process is determined by its biological effect. IFN-gamma activates the production of pro-inflammatory cytokines. This circumstance should be taken into account when determining treatment strategies and tactics. The method of choice in this system is complex anti-inflammatory and immuno-corrective therapy.

When performing surgery on the middle ear in patients with CPOM and TSC, two goals were pursued - sanitizing the cavity of eardrum and preventing the strengthening of sclerosis process, and reconstructing the elements of sound-conducting system in order to preserve and improve hearing in patients. When choosing the volume of surgical intervention, the prevalence and localization of the sclerotic process the degree of changes in the middle ear, were taken into account. For patients the operations were carried out in one or two stages, taking into account the above criteria.

Based on the surgical approach, the patients were divided into 3 groups: group 1 included 18 patients, 4 of them had surgery performed

through endo-aural access through the ear funnel; group 2 included 26 patients, 5 of them had surgery performed through endo-meatal access; for the rest of patients the tympanic plasty and other types of surgical interventions were performed through behind-the-ear access. The 3rd group consisted of 22 patients (combination of cholesteatoma with tympanic sclerosis) and all types of surgical interventions were performed through post-auricular approach.

The patients were undergone several types of surgery; more than half of the patients underwent various types of tympanic plasty.

The tympanic plasty without use prostheses was performed in 6 (54.5%) patients, 16 (24.2%) patients used partial and complete osseous prostheses made of titanium (4; 6.1%) and Teflon (12; 18.2%). Other types of interventions were sanitary surgery with closed tympanic plasty in 17 (25.7%) patients, revision of the tympanic cavity with osseous plasty in 5 (7.57%) patients (7.57%) and 5 (7.57%) patients.) patients undergoing myringoplasty and atticoanthrotomy with plastic surgery of lateral wall of the attic in 1 (1.5%) patients. If the result of surgical intervention was unsatisfactory - anatomical (3; 4.5%) or functional (5; 7.54%) -the repeat operation was performed, during which the identified violations were eliminated. During reoperation, the remobilization of auditory ossicles (4; 6.06%) or correction of prosthesis position (3; 4.54%) was most often performed; in 1 (1.51%) patient the prosthesis was replaced with the longer one that was more suitable in type. In the postoperative period, the symptomatic therapy was carried out depending on the health state, as well as local therapy. For a week, the restorative and anti-inflammatory treatment was carried out, the antibacterial, anti-

inflammatory and analgesic drugs were prescribed parenterally. The antibacterial therapy was prescribed for 5-7 days, the drug of choice was cephalosporins - cefazolin or ceftriaxone at a dose of 1.0 g 2 times a day I/M or I/V. All patients were prescribed anti-edema and dehydration therapy in the first 3-5 days. The corticosteroids were used in a short course, lasting 3-5 days, usually prescribing dexamethasone at an initial dose of 12 mg once a day IM with a dose reduction according to the scheme 12 - 8 - 6 - 4 - mg. For anti-inflammatory purposes, they prescribed calcium gluconate 10%-10 ml + NaCl 0.9%-100 ml, intravenous drip.

To prevent postoperative relapses of tympanic sclerosis during the rehabilitation

period, the method of administering the drug Longidase using ultrasound –

phonophoresis - was developed. Phonophoresis with oscillation frequency of 880

kHz began after surgery on the 3rd day. After each procedure, the operated ear was

bandaged in a surgical dressing room, according to generally accepted rules

. Localization of exposure was the peri-temporal region. The direct contact, contact

medium dry substance of the drug “Longidase 3000ME” was diluted immediately

before the procedure at 5.0-7.0 g. medical vaseline oil for ultrasonic exposure and

applied to skin near the temporal region. Pulse power flux density mode 0.4-0.7

W3. Pulse duration 10 ms; labile (movable) contact technique. The duration of the

procedure is 10-15 minutes daily, once a day. The course of therapy includes 10

effects.

Patients with an advanced form of SCT (n=26) received complex treatment using local UST therapy with the anti-fibrotic drug Longidase. In the limited form (n=18), patients underwent the following measures: standard treatment was performed - anti-inflammatory, antibacterial therapy, ear drops, physical therapy using the same method. Physiotherapeutic treatment started after surgery on the 3rd day. After each procedure, the operated ear was bandaged surgical dressing room, according to generally accepted rules. When cholesteatoma was combined with tympanic sclerosis, patients (n=22) underwent the following corrective measures: this is standard treatment - anti-inflammatory, antibacterial therapy, ear drops and dressings of the operated ear.

The effectiveness and tolerability of complex treatment were assessed after 10 days of treatment. It should be noted that a correct understanding of the mechanisms underlying the development of tympanic sclerosis allows us to adequately assess the required volume of surgical and therapeutic care in each specific case and avoid possible mistakes.

The results of studies conducted to study the dynamics of pro- and anti-inflammatory cytokines as a result of the treatment measures showed that not only positive dynamics were observed clinical parameters, but also the levels of the studied cytokines in the blood serum. In patients with a limited form of TSC, the level of IL-1β after the measures increased relative to the indices before treatment ($P<0.001$); in patients with a widespread form of TSC, after treatment the level of IL-1β decreased by 1.2 times relative to the indicators before treatment ($P< 0.001$). In patients with TSC with cholesteatoma, it also significantly decreased relative to the initial values ($P < 0.001$). The level of IL-10 after the treatment measures also showed positive dynamics. A significant decrease in this cytokine was observed in patients with a limited form of SCT relative to the initial values ($P<0.001$), with widespread SCT ($P<0.001$). Changes in the synthesis of IL-10 as a result of corrective measures also affected patients with tympanic sclerosis against the background of cholesteatoma ($P<0.001$).

IFN-γ is secreted by several immune cells, including macrophages, NK cells, and T cells, and play a role in directly stimulating major inflammatory effector cells. In our studies, hypersecretion of interferon-γ was observed in tympanic sclerosis, and the maximum value was observed in patients with a common form of tympanic sclerosis ($P<0.001$). In patients with a limited form of TSC, there was a significant decrease in the level of IFN-γ relative to the initial values ($P<0.02$). A significant decrease in this interleukin was noted in group III of patients ($P<0.001$).

Also, the effectiveness and tolerability of complex treatment were assessed by the dynamics of the following clinical indices: reduction of pain, postoperative cessation of exudation from the surgical area, reduction of hyperemia of the surgical area, and reduction of local edema.

The additional use of UST + Longidase made it possible to significantly increase the number of patients assessing their quality of life as “good” or “excellent”. Surveys of patients were conducted upon admission to the hospital and after completion of course for physiotherapy. During treatment with Longidase, the more pronounced positive changes in health-related life quality indices were noted: in the majority of patients, the psychological health improved.

The effectiveness and tolerability of complex treatment were assessed after 6-
12 months by the dynamics of following indices: relapse of TSC, effectiveness of
therapy, and the frequency of inflammatory diseases of the upper respiratory tract
over the past year. A positive aspect of using Longidase in combination with basic
therapy was a decrease in the body’s susceptibility to viral and bacterial agents,
which was noted by almost all patients receiving Longidase. This leads to a
decrease in the incidence of diseases of the upper air tract, sinusitis, eustachitis,

chronic otitis, and also reduces the development of various inflammatory processes in the middle ear, relapses of the disease and number of complications. Taking into account the modern understanding of the pathogenesis and patho-morphology of tympanic sclerosis, it is advisable to use UST with Longidase only in the treatment of this disease, but also for the purpose of preventing sclerotic changes in the middle ear and tympanic cavity and after surgery.

Longidase increases the bioavailability of drugs, prolongs the action of hyaluronidase, and also suppresses inflammatory reactions, reduces the stimulating development of the fibrotic process, which makes it possible to use it for the prevention and correction of fibrosis and sclerosis, dystrophic changes in the cavity of the eardrum. For the same reason, Longidaza reduces the risk of relapses and re-fixation of the stapes, which significantly reduces the frequency of hospitalization due to relapses of TSC. TPA data were also assessed over time 12 months after surgical and rehabilitation therapy.

According to TPA data, the patients of all groups had significantly improved hearing relative to the initial values ($P < 0.001$); the more pronounced improvement in hearing was observed in patients of groups II and III.

In patients of group III after treatment, the indices were also improved, but to a slightly lesser extent in comparison with groups I and II. The indicators after treatment also remained relatively high in comparison with group I ($P<0.05$) and group II ($P<0.05$).

After taken therapy the significant improvement in the degree of hearing impairment was noted. Thus, in patients of all study groups before therapy the normal values of TPA were not detected, but after therapy in patients of group I, the normal values were already noticed in 16 (88.9%) patients, in group II in 19 (73.1%) patients, and in group III group in 7 (31.8%) patients ($P<0.001$). After rehabilitation therapy, the grade IV was no longer detected in the study groups, and, only in group III patients the grade III hearing loss was observed. It should be noted that the data before and after treatment were considerably significant ($P<0.05$).

PRACTICAL RECOMMENDATIONS

1. In order to prevent the formation of sclerotic changes in the tympanic cavity during chronic inflammatory processes, as well as the recurrence of these phenomena after surgical interventions for TSC, it is advisable to study blood and ear swabs for the content of interleukins IL-1β, IL-10 and INF-γ in order to determine immunological changes and its subsequent correction, which will avoid repeated surgical interventions.

2. Rehabilitation therapy in the postoperative period should be carried out comprehensively, including phonophoresis using the drug Longidaza, which contributes to a more rapid improvement of clinical, immunological and audiological parameters, and reduces the risk of relapse of sclerotic processes.

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