ORIGINAL ARTICLE

Correlation between Proinflammatory Cytokine Levels and Scored Clinical Parameters in Patients with Secretory Otitis Media

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OBJECTIVE: Purpose of this study was to establish paired correlation between IL6, IL8, IFNγ, TNFβ, TNFα, IL1β levels in samples from middle ear secretion and scored clinical parameters of secretory otitis media.

METHODS: Fifty-nine patients took part in the research (totalling 108 samples) age up to 15 years old with secretory otitis media (SOM), without other diseases. Cytokine concentrations were measured using specific enzyme-linked immunosorbent assays (ELISAS).

RESULTS: Percentage of detectable cytokines in the middle ear samples ranged from 100% for TNFα and IL1β to 18% for IFNβ. IL8 levels were highest in patients with the mucous secretion type. The IFNγ were higher in patients with retracted eardrum than in those with thinned eardrum and preserved eardrum.

CONCLUSION : The levels of IL6, IL8, IFNγ, TNFβ, TNFα and IL1β were found to correlate with clinical parameters of secretory otitis media.

Secretory otitis media (SOM) is the most common cause of the acquired hearing impairment. Besides the advance in the diagnosis and treatment, the incidence of secretory otitis has been increasing in the last twenty years. The facts show that more than 80% of children have had at least one episode of the secretory otitis until three years old, and 40% of them have had three and more episodes of this disease [1]. SOM is distinguished by the retention exudates of the different density. The reason for the treatment failure is probably partial knowledge of etiopathogenetic molecular mechanisms responsible for the beginning and the course of the secretory process in the mucous membrane of the middle ear.

The components of the bacteria and viruses that locally colonize the epithel or adenoids of the upper respiratory tract are the most likely originator of inflammation process, which results into cell metaplasia and different mucin secretion of the middle ear. Cytokine identification with pro-inflammatory effect, IL1β, TNFα [2], IL6 [3] and IL8 [4] in secretion of the middle ear of the patients with SOM indicates that in these processes, the inflammatory mediators take the leading if not the key part. Interleukin 1β and TNFα induce the IL-8 production that is responsible for the accumulation of leukocytes, primarily polimorfonucleares and T lymphocites. Uncontrolled local production of these mediators is considered to lead to unregulated activation of the inflammatory cells, and the consequential production of metalloproteinase, which altogether with the high concentrations of IL1β, TNFα and IL8 results in tissue impairment. Uncontrolled local production and manifestation of activities of inflammatory mediators with consequential tissue impairment could also be a result of insufficient production and effect of mediators with anti-inflammatory effect. Interleukin 10 stops the production of pro-inflammatory mediators from the activated monocytes and polimorfonucleares, which is the reason of having been considered to manifest protective effects in the conditions of uncontrolled inflammation, what has been demonstrated in the sequence of experimental models of pancreatitis, uveitis, keratitis, hepatitis and peritonitis [5]. On the other hand, excessive production of IL10 in the beginning phase of microbe colonization result in later inadequate immune answer, which allows intensive replication of infectious agens and therefore more aggressive inflammation process [6]. In addition to IL10, factor of transformation of increase beta - 1 (TGFβ1) is cytokine which stops originated inflammation process and which is exceedingly produced in case of the recurrent inflammation process resulting in stimulation of secretion of extracell matrix and local tissue fibrosis [7].

In therapeutical and prognosis sense, the most significant form of SOM is that which is recurrent, that is, maintained after applied therapy. Finding predictors of the chronicity of SOM endurance, which are still unclear enough, is the only way to recognise the forms of diseases that require more active attitude towards concept of treatment (usage of antibiotics and corticosteroids not according to the protocol, implantation of tubes for long ventilation).

Considering everything mentioned above, with the planned research, we decided to find presence of IL6, IL8, IFNγ, TNFβ, TNFα and IL1β in excaudate of the middle ear and compare the findings with the established clinical and functional alterations.

MATERIALS AND METHODS

The research included 59 patients of the both sex, age up to 15 years old, who were diagnosed secretory process of the middle ear - secretory otitis media (SOM), based on the standard diagnostic procedures without any other diseases and disturbance.

The following clinical and functional disturbances were scored for the patients who took part in the research:

- impairment level of the middle ear structures as recognised by the otomicroscopic check;
- level of hearing impairment as determined by tonal liminary audiometry;

- rigidity of the middle ear as evaluated by tympanometry;
- and density of secretion in the middle ear as determined by inspection during taking secretion samples from the middle ear at the opening of eardrum for implantation of tubes.

The patients have been divided according to the following clinical and functional disorders:

* SOM type: SOM1: the group of patients with isolated secretory process, SOM2:the group of patients with SOM and SOM3: adenoid vegetations and the group of patients with residual SOM);
* Endurance of secretory process (the group in which SOM lasts for less than three months; the group in which SOM lasts for longer than three months);
* Degree of the hearing impairment (the group with conductive hearing impairment up to 40 dB, the group with conductive hearing impairment above 40dB with or without sensorineural component of hearing impairment);
* Finding of acoustic impedancemetry (the group with the finding of tympanogram - type "B", the group with the finding of negative tympanogram - type "C");
* Eardrum appearance (the group of patients with preserved, the group of patients with thinned and the group of patients with retracted eardrum).

With all patients, the microsurgery intervention has been conducted under condition of general endotracheal anesthesia, paracentesis with implantation of aerotubes. The eardrum has been opened in the anterior-inferior and anterior-superior quadrant and secretion has been taken by the sterile aspirator (Juhn - Tym - Tap aspirator, Xomed Products). Secretion has been taken from both ears. The whole secretion volume has been removed into the capped plastic test tube (total volume 1,5 ml, Eppendorf, USA), which has previously been filled with 0,5 ml medium (RPMI, ICN, USA). Secretion samples have been frozen at -70°C until testing. All cytokine concentrations in the samples of exudates of middle ear have been determined with commercial tests (FlowCytomix, Bender MEDSYSTEMS, USA) on the Flow Cytometer (Beckman Coulter XL-MCL, USA).

In the result analysis, Fisher's parametric analysis of variance has been used for comparison of three or more groups of data (ANOVA) for parametric and analysis of variance for proportions of nonparametric data. Relationship between parameters were established using Pearson's coefficient of linear correlation (r) , since our parameters were tested and confirmed to have normal distribution (using Kolmogorov-Smirnov test), α error was 0.05, and β 0.80.

RESULTS

Examined cytokines have not been detectable with equal frequency in all samples. The percentage of the samples in which cytokines could have been detected has been in the range of 18% for detectable values of IFNγ, to 100% for detectable values of TNFα and IL1β.

In our study group, we have had 26 patients with the residual of secretory otitis besides previous implantation of tubes. The highest average concentrations of IL6, interferon gamma have been found exactly in this group (Table 1), while the concentration of IL8 has been the highest in the group of patients without adenoid vegetations and residual. The concentrations of TNFα and TNFβ have been considerably higher ($p<0.05$) in the group of patients with secretory otitis media (SOM) and vegetations, while the average value of IL1β has been the highest in the group of patients with the first type of secretory otitis media (SOM), although without statistical significance. When the measured individual values of the mentioned cytokines (IL6, IL8, IFNγ, TNFβ, TNFα, IL1β) and paired correlation in all examined samples have been analyzed, the concentrations of IL6 and IL8 were found to correlate with each other in the groups of patients with SOM with or without adenoid vegetations (Table 2). In the groups of patients with

Table-1: The values of cytokines (average value ± standard deviation, pg/ml) in the samples of the patients with secretory otitis media listed according to the type of secretion, type of SOM, eardrum appearance and the hearing impairment level.

	secretion in cavum		SOM			eardrum appearance			hearing impairment level	
	mucous	**serous**	**type 1**	**type 2**	**type 3**	**preserved**	**retracted**	**thinned**	**< 40dB**	**> 40 dB**
IL6	159 ± 211	1644 ± 2675	720 ± 1336	235 ± 216	2486 ± 3187	1087 ± 2204	679 ± 1014	67 ± 14	1386 ± 2688	121 ± 145
IL8	**5310 ± 8215***	720± 1000	8830 ± 5462	3166 ± 7679	1158 ± 25301	7990 ± 16073	5516 ± 9223	1981 ± 3888	598 ± 1425	2688 ± 3867
IFNγ	185 ± 217	77 ± 37	265 ± 404	188 ± 285	646 ± 1279	**49 ± 37 ***	153 ± 227	3 ± 7	91 ± 72	318 ± 47
TNFβ	1460 ± 3587	1313 ± 1715	962 ± 1411	**1676 ± 3384***	577 ± 780	1012 ± 1522	1022 ± 1562	1421 ± 1290	1192 ± 1591	1196 ± 1936
TNFα	3217 ± 11467	388 ± 631	245 ± 544	**1653 ± 4227***	132 ± 175	2587 ± 10411	858 ± 2157	190 ± 186	630 ± 1826	115 ± 100
IL1β	543 ± 995	519 ± 1183	623 ± 1024	518 ± 982	**147 ± 98 ***	**784 ± 1456 ***	257 ± 324	523 ± 904	594 ± 1201	710 ± 955

***: significance level P<0.05**

SOM type1 - isolated secretory type; SOM type2 - SOM and adenoid vegetations; SOM type3 - SOM residual

Table-2: Profiles of the paired correlation of the produced cytokines in the samples of the patients with different type of SOM (R - Pearson correlation coefficient, p - significance coefficient).

SOM1	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,874 p = 0,000	NS	NS	NS	NS
IL8	R = 0,874 p = 0,000		NS	NS		
IFNγ	NS	NS		NS	NS	NS
TNFβ		NS	NS		NS	NS
TNFα	NS	NS	NS	NS		R = 0,952 p = 0,000

SOM2	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,424 p = 0,005	R = 0,307 p = 0,048	NS	R = 0,653 p = 0,000	R = 0,473 p = 0,002
IL8	R = 0,424 p = 0,005		NS	NS	R = 0,317 p = 0,038	R = 0,394 p = 0,009
IFNγ	R = 0,307 p = 0,048	NS		NS		
TNFβ		NS	NS		NS	NS
TNFα	R = 0,653 p = 0,000	R = 0,317 p = 0,038	NS	NS		R = 0,841 p = 0,000

SOM3	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		NS	NS	NS	R = 0,406 p = 0,040	R = 0,945 p = 0,000
IL8	NS		NS	NS	R = 0,963 p = 0,000	NS
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		NS	NS
TNFα	R = 0,406 p = 0,040	R = 0,963 p = 0,000	NS	NS		NS

NS: Non Significant

Significance levels (P<0.01 and P<0.05)

Table-3: Profiles of paired correlation of the produced cytokines in the samples of the patients with different type of secretion (R - Pearson correlation coefficient, p - significance coefficient).

mucous	IL6	IL8	IFNγ	TNFβ	TNFα	IL1β
IL6		R = 0,672 p = 0,000	NS	NS	NS	NS
IL8	R = 0,672 p = 0,000		NS	NS	NS	NS
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		NS	NS
TNFα	NS	NS	NS	NS		R = 0,825 p = 0,000

serous	IL6	IL8	IFNγ	TNFβ	TNFα	IL1β
IL6		NS	NS	NS	NS	R = 0,763 p = 0,000
IL8	NS		NS	NS	NS	R = 0,388 p = 0,037
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		NS	NS
TNFα	NS	NS	NS	NS		R = 0,586 p = 0,001

Significance levels (P<0.01 and P<0.05)
NS: nonsignificant

SOM with vegetations or residual, the concentrations of IL8, TNFα and IL1b had a good correlation, Only correlation between the values of IFNγ and IL6 was found in the group of patients with SOM and vegetations,

Relating to the type of secretion found in the middle ear, we have determined the concentrations of IL6, IL8, IFNγ, TNFβ, TNFα and IL1β in 64 mucous secretion samples and 29 serous secretion samples. The only significant difference has been found for concentrations of IL8, which have been higher in the mucous secretion samples. Furthermore, concentrations of IFNγ and TNFα have been higher in mucous secretion samples while the values of IL6 have been higher in the serous secretion samples (without statistical significance). The levels of TNFα and IL1β have been almost identical regardless of the type of secretion. Table 3.

When we have determined average cytokine concentrations between groups with the different type of tympanogram we have found the considerable differences in the levels of IL6, IL8, TNFβ and TNFα. The participants with tympanometric finding of type "B" have had considerably higher average values of IL6 in relation to the participants with tympanometric finding of type "C". Furthermore, the average levels of IL8 and TNFβ have been considerably higher in the group of patients with tympanometric finding of type "B" and mucous secretion in comparison to the patients with tympanometric finding of type "C" and serous secretion. Contrary to this finding, the values of TNFα have been considerably higher in the secretion samples with tympanometric finding of type "C".

Analysis of concentrations of IL6, IL8, IFNγ, TNFβ, TNFα and IL1β, has shown that there are no statistically considerable differences between average values of the samples of patients with the different

level of hearing impairment (Table 1). The values of IL8, IFNγ and IL1β have been higher with the patients with conductive reduction higher than 40dB, while the values of IL6 and TNFα have been higher with the patients with the hearing impairment lower than 40dB, with almost identical average concentrations of TNFβ in both groups. According to the measured concentrations, the best predictor of hearing impairment are the levels of IL8 and in the way that increasing of the values leads to more serious level of hearing impairment. In the samples of both examined groups we have found the same profile of the considerable correlation of the produced cytokines, which are the values of IL8 and IL6, actually IL1β and TNFα. However, in the samples of the group of patients with more serious level of hearing impairment we have found the existence of the additional considerable correlation, between the values of ILβ and IL1β (Table 4).

The comparison of the average values of the examined cytokines in the groups of patients with SOM, divided according to the appearance of eardrum, has shown the considerable increase of IFNγ concentration in the patients with the retracted eardrum. Therefore, the lowest values are found in the patients with the retracted eardrum ($p<0.05$, Table 5). The values of IL1β have been considerably highest in the patients with the preserved eardrum ($p<0.05$), as well as the values of IL6, IL8 and TNFα, but without statistical significance. In the samples of all three examined groups of patients, we have found the same profile of significant paired-correlation of the produced cytokines, which are the values of IL8 and IL6, actually IL1β and TNFα. However, in the group of patients with the retracted eardrum the values of TNFα and TNFβ considerably correlate, whereas in the samples of the group with retracted eardrum, there is considerable correlation between the values of IL6 and TNFα, actually between the concentrations of IL8 and TNFβ.

Table-4: Profiles of paired correlation of the produced cytokines in the samples of the patients with the level of hearing impairment (R - Pearson correlation coefficient, p - significance coefficient).

< 40 dB	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,675 p = 0,000	NS	NS	NS	NS
IL8	R = 0,675 p = 0,000		NS	NS	NS	NS
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		NS	NS
TNFα	NS	NS	NS	NS		R = 0,897 p = 0,000

> 40 dB	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		NS	NS	NS	NS	R = 0,771 p = 0,000
IL8	NS		NS	NS	NS	R = 0,538 p = 0,000
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		NS	NS
TNFα	NS	NS	NS	NS		R = 0,552 p = 0,000

Significance levels ($P<0.01$ and $P<0.05$)
NS: Non significant

DISCUSSION

In our research, we have determined the concentration of IL6, IL8, IFNγ, TNFβ, TNFα and IL1β in the middle ear secretion with SOM children.

Pro-inflammatory cytokines TNFα and IL1β have been determined in all 108 samples, whereas TNFβ has been detected in 90% of the samples, while IL8 and IL6 have been detectable in 61% and 44% of the secretion samples. Maxwell and his associates [11] have shown in their study on 36 samples that the IL8 results have been positive in 92% of the samples, IL1β in 67% and TNFα in 77% of the samples. The authors of this study have not determined TNFβ, unlike our results where TNFβ has been detected in 90% of the samples and with an average value of 719 ± 109 pg/ml. Yellon and his associates have detected IL1β in 58%, IL6 in 83%, IFNγ in 61% and TNFα in 38% of 75 analyzed

Table-5: Profiles of the paired correlation of the produced cytokines in the samples of the patients with different eardrum appearance (R - Pearson correlation coefficient, p - significance coefficient).

preserved	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,411 p = 0,002	NS	NS	NS	R = 0,610 p = 0,000
IL8	R = 0,411 p = 0,002		NS	NS	NS	R = 0,433 p = 0,001
IFNγ	NS	NS		NS	NS	
TNFβ	NS	NS	NS		NS	
TNFα	NS	NS	NS	NS		R = 0,673 p = 0,000

retracted	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,988 p = 0,000	NS	NS	NS	NS
IL8	R = 0,988 p = 0,000		NS	NS	NS	NS
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	NS	NS		R = 0,786 p = 0,000	R = 0,578 p = 0,005
TNFα	NS	NS	NS	R = 0,786 p = 0,000		R = 0,784 p = 0,000

thinned	**IL6**	**IL8**	**IFNγ**	**TNFβ**	**TNFα**	**IL1β**
IL6		R = 0,755 p = 0,012	NS	NS	R = 0,779 p = 0,008	R = 0,940 p = 0,000
IL8	R = 0,755 p = 0,012		NS	R = 0,822 p = 0,004	NS	NS
IFNγ	NS	NS		NS	NS	NS
TNFβ	NS	R = 0,822 p = 0,004	NS		NS	NS
TNFα	R = 0,779 p = 0,008	NS	NS	NS		NS

Empty cells are nonsignificant
Significance levels (P<0.01 and P<0.05)

middle ear secretion samples [13]. Based on 66 middle ear secretion samples of those ill with SOM, in his study Johnson [8] has come to the results that coincide with those in our research with regard to the incidence of pro-inflammatory cytokines in the secretion. According to the results of this study, the incidence of IL8 has been 100% whereas TNFα and IL1β have been detected in 91% and 97% of the middle ear samples. The mentioned pro-inflammatory cytokines in the majority of the tested middle ear samples of patients with a different type of SOM secretion, appearance of the eardrum and a hearing-impaired level show that both these and other mediators are crucial regulators of local molecular processes which lead to pathological changes. The role of predisposed factors is overemphasized (a dysfunction of Eustachian tube, an adenoid hypertrophy, an allergic manifestation and gastroesophageal reflux).

The results of our research have shown that the concentration of IL8 is significantly higher in the mucous samples of middle ear secretion. The highest concentration is found in the samples of the patients with the SOM secretion type without adenoid vegetations and with a preserved appearance of the eardrum, which is the best predictor of hearing-impaired level in comparison to all tested cytokines. The only research so far, conducted by Russeau and his associates [16], in which the correlation between a level of cytokines and hearing-impaired level has been tested out, has shown a significantly positive correlation between IL6 and a hearing-impaired level. In the middle ear secretion samples of our patients divided into groups based on a hearing-impaired level, IL6 and IL8 levels significantly correlate as well as IL1β and TNFα. The coefficients of the IL6 and IL8 correlation have been almost twice as high in the samples of the group of patients with a conductive hearing impairment less than 40 dB (Table 5.). However, in the samples of patients with hearing impairment more than 40 dB, we have also found significant correlations between IL8 and IL1α. On the basis of the past researches, it has been assumed that goblet cells are central effectory cells in the pathogenesis of SOM since they produce IL8 and mucin as a result of the stimulation by the pro-inflammatory cytokines TNFα and IL1β [10]. Under in vitro conditions, the result of the stimulation of HT29-MTX goblet cells by the cytokines TNFα, IL6 and IL8 has been the production of mucin. The resulting mucin has been the longest-lasting after being stimulated by IL8, almost twice longer when stimulated by IL6, and three times longer in response to the stimulation by TNFα [11]. IL8 also influences goblet cells while stimulating and maintaining a lasting production of mucin, thus it could lead to the chronic inflammation process and maintaining chronic secretory process [12]. It was proved that a mucous secretion contains significantly higher concentration of IL8 in relation to a serous and purulent middle ear secretion with SOM patients [13]. Mucin is main secretory component whose concentration determines physical characteristics of secretion, of which viscosity is the most significant [14]. In our researches, average concentrations of IL8 have been the highest in mucous middle ear secretion samples, then in the samples of patients with secretory otitis media (SOM) without vegetations and relapses as well as in the samples of patients with an unimpaired eardrum and in those of patients whose hearing impairment level has been more than 40dB. Furthermore, the values of IL8 have been significantly related to those of IL6 in the middle ear secretion samples of patients with SOM with or without vegetations, in the mucous, but not in the serous samples of patients as well as in the samples of patients with a smaller hearing impairment (to 40dB). However, the values of IL8 significantly correlated with TNFα and IL1β values in the samples of patients with SOM) vegetations and recurrent form of secretory otitis media (SOM. They also correlated with TNFβ values in the samples of patients whose eardrums were either retracted or thinned, as well as with the values of IL1β in the samples of patients with a severe hearing impairment (more than 40 dB). The significant correlation between the values of IL8 and

IL6 in less severe clinical forms of SOM, i.e. a correlation between IL8 and TNFβ, TNFα, IL1β in severe forms of SOM indicates that different cell populations dominate in different forms of a secretory process in the middle ear. Based on a significant production of pro-inflammatory cytokines, we have seen that polymorphonuclear leukocytes and macrophages, which cause a local inflammation and an impairment of middle ear structures, dominate in the severe clinical forms of SOM with a hard functional hearing impairment.

In our testing, the values of a gamma interferon (IFNγ), of the crucial TH1 cytokine, have been higher in the middle ear samples of patients with a mucous secretion, who have had recurrent form of SOM, a retracted eardrum and a higher hearing level loss. Past researches showed that the values of IFNγ do not correlate with a repeated implantation of aeration tubes, i.e. with a recurrent form of SOM [13]. When comparing the individual values of the tested cytokines (IL6, IL8, IFNγ, TNFβ, TNFα, IL1β) in the same sample, the only significant correlation was between IFN_ and IL6 (R= +0,307, p= 0,048) and only in a group of patients with recurrent form of SOM. Yellon and his associates have not found any significant correlation between the values of IFNγ and IL6 and of TNFα and IL1β although, they have found a highly significant correlation between IL6, TNFα and IL1β in the middle ear secretion samples of patients with SOM [15].

The average values of TNFβ were highest in the samples of patients with secretory otitis media (SOM) and adenoid vegetations as well as in the samples of patients with a retracted eardrum. The values of TNFβ have been approximately equal in the samples of the groups of patients with a different hearing impairment level and a different quality of middle ear effusion. However, the highest values of TNFα have been found in secretory otitis media (SOM) group with vegetations, with mucous middle ear effusion, as well as in the samples of patients with a preserved appearance of the eardrum and a smaller hearing impairment. The results that show significantly higher average concentrations of TNFα in the samples of a group with a specified indication for an adenoid operation are expected, i.e. an inflammatory response is quite acute in adenoiditis. The values of TNFα and IL1β are considered the markers of the acute inflammatory response while high local concentrations of IL8 are connected with a chronic middle ear process [16]. It is likely that the local production of TNFα and IL1β is stimulated by endotoxin that, thus indirectly induces the acute phase of the inflammatory response, but also an increase in the osteoclast activity and the stimulation of a fibroblast proliferation. Eustachian tube obstruction can be the result of the effect of such mediators, released from inflammatory cells in the nose and epipharynx mucoses. Inflammation processes in the nose mucous membrane and that of epipharynx (adenoiditis) can cause longitudinial obstruction of a tube that is responsible for an induction and preservation of chronic secretory otitis. An endotoxin that remains in the middle ear even after the elimination of viable bacteria by an antimicrobial treatment and the defense mechanism of a patient represents a potent stimulator of the inflammatory cytokines production, which stimulates and preserves secretory otitis as a chronic, asymptomatic and nonsuppurative form of otitis media.

CONCLUSION

The results of this research have shown that, due to the correlation with clinically recognisable forms of SOM, determining the concentration of IL6, IL8, IFNγ, TNFα, TNFα and IL1β enables the identification of the predictor of the severe forms of illnesses in terms of established clinical and functional alterations.

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