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THE HEAT SHOCK PROTEIN 70-2 GENE (RS1061581) ASSOCIATES WITH THE ACUTE OTITIS MEDIUM IN CHILDREN

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Summary

Acute otitis media (AOM) represents one of the most prevalent pediatric conditions worldwide. Affecting millions of children / adolescents each year, AOM constitutes a significant public health concern. Although the fundamental mechanisms underlying AOM development are understood, the molecular and genetic aspects of its pathogenesis remain insufficiently explored.

The Aim *of this study is to investigate the association between the HSP70-2 gene (rs1061581) A1267G polymorphism and AOM in children, as well as to evaluate the inheritance patterns of the disease and the risks associated with the severity of AOM in the studied cohort.*

Materials and Methods. *A prospective cohort study was conducted involving 95 children with AOM, aged 7 to 18 years. The cohort comprised 34.74% (n=33) girls and 65.26% (n=62) boys. The study adhered to the principles of Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and biomedical ethics standards for scientific research involving human participants. Informed consent was obtained from the parents or guardians of each child. Participants were stratified by age (7-11 years (n=81) and 12-18 years (n=14)), AOM severity (severe – 45.26% (n=43), non-severe – 54.74% (n=52)), and the nature of mucosal inflammation (catarrhal – 52.63% (n=50), purulent – 47.37% (n=45)). A control group of 50 healthy children was included, consisting of 20 girls (40.0%) and 30 boys (60.0%). The groups were age-matched (p>0.05). The HSP70-2 (rs1061581) gene polymorphism was analyzed using qualitative polymerase chain reaction. Risk assessment was performed using Risk Ratio, Odds Ratio, and 95% Confidence Intervals.*

Results. *The mutation frequency of the heat shock protein gene HSP70-2 (rs1061581) in children with AOM from Northern Bukovina was 35.79% (8.42% in homozygous state), which was 11.79% higher than in healthy children (χ^2=4.20; p=0.04). The distribution of HSP70-2 (rs1061581) genotypes in the studied cohort generally conformed to the Hardy-Weinberg equilibrium (χ^2=1.36; p=0.243) and did not deviate in allele frequency from the average values observed in Caucasian populations (PA=0.24-0.36; PG=0.64-0.76). Binary logistic regression analysis proved a significant probability of AOM development in A-allele carriers' children under both dominant and additive models (OR=2.01; 95%CI: 1.01-4.06; p=0.05 and OR=2.01; 95%CI: 1.10-3.77; p=0.03), with the lowest out-of-sample Akaike prediction coefficients (AC=16.67 and 15.33).*

Epidemiological analysis confirmed an almost twofold increased risk of AOM in children with A-allele of the HSP70-2 gene (rs1061581) (OR=1.76; OR 95%CI: 1.02-3.05; p=0.026), with the lowest chances in G-allele carriers, especially in the homozygous state (OR=0.50; OR95%CI: 0.25-0.99; p=0.035). Furthermore, the risk of severe AOM increases more than 7 times for purulent discharge from the ear at the age of 7-11 years (OR=7.29; OR 95%CI: 1.44-37.01; p=0.045) with low chances of its development at the pubertal age (12-18 yo) (OR=0.14; OR 95%CI: 0.03-0.70; p=0.019).

Conclusions. *The A-allele of the HSP70-2 gene (rs1061581) is associated with an almost twofold increase in AOM risk in the studied pediatric cohort. The risk of severe AOM increases more than sevenfold in cases of purulent ear discharge among children aged 7-11 years*

Key words: *Acute Otitis Media; HSP70-2 gene (rs1061581); Children; Heat Shock Protein; Risks; Inflammation; Disease severity*

Introduction

Acute otitis media (AOM is one of the most common pediatric conditions worldwide. Affecting millions of children and adolescents annually, AOM represents a significant public health burden [1; 2]. According to the World Health Organization (WHO), AOM is a leading cause of healthcare visits and antibiotic prescriptions in pediatric populations [3; 4]. Approximately half of all antibacterial drugs prescribed globally are for AOM treatment, despite the fact that antibiotic therapy is not always warranted [5]. AOM is characterized by inflammation of the mucous membranes within the middle ear cavities, particularly the tympanic cavity and the eardrum (ED) [6]. However, the mechanisms underlying severe otitis media under similar external conditions, influenced by individual immunological, anamnestic, and microsocial factors, remain inadequately understood. Furthermore, the role of genetic predispositions in AOM development is poorly elucidated.

Among the diverse factors and mechanisms contributing to nonspecific resistance and specific immune reactivity in the context of AOM, heat shock proteins (HSPs) are of particular interest. HSP synthesis represents a universal cellular stress response, facilitating chaperone functions (binding hydrophobic damaged peptide sites and their repair), protein folding (maintaining the normal structure of proteins inside the cell and preventing aggregation), and participation in immunoregulatory processes, including cytokine production [7-12]. HSPs also play a role in immune adaptation by transporting antigenic peptides from infected or tumor cells, thereby enabling immune surveillance [13; 14]. HSPs are categorized into high molecular weight (HSP100, 90, 70, 60, and 40 kDa) and low molecular weight (HSP25 and 10 kDa). Among these, constitutive HSP70c and inducible HSP70i are distinguished, with the latter being produced in response to external stressors. Inducible HSP70i proteins are encoded by the genes HSP70-1 (OMIM:140550), HSP70-Hom (OMIM:140559), and HSP70-2 (OMIM:603012) [15; 16].

Single nucleotide polymorphisms (SNPs) in the HSP70 gene influence its transcriptional activity, leading to altered protein function and subsequent modifications in stress response mechanisms and other pathological

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conditions. The replacement of G (guanine) by A (adenine) on chromosome 6 (6p21.33; chr6:31816809; GRCh38.p14) at position 1267 of the HSP70-2 gene (synonymous variant HSPA1A, 2KB upstream variant, where transcription occurs earlier – HSPA1L and HSPA1B) leads to changes in the level of HSP70-2 mRNA expression (rs1061581). This alteration may increase susceptibility to inflammatory diseases [16], coronary heart disease (CHD) [17], systemic arterial hypertension [18], idiopathic pulmonary fibrosis [19], lymphoblastic leukemia [20], pneumoconiosis [21], multiple sclerosis inflammation [22], preeclampsia [23], duodenal ulcer and gastric cancer [24], enhance oxidative stress activity in diabetes mellitus [25], among other conditions.

Despite extensive research into the etiology and clinical progression of AOM, particularly in pediatric populations, there is currently no evidence regarding the involvement of HSP70 family genes in the pathogenesis of acute otitis media. At the outset of this study, the genetic and molecular aspects of AOM development, particularly in relation to the immunological response of the macro organism, remained unexplored. Consequently, we aimed to investigate the genetic mechanisms underlying AOM formation, focusing on the association with the HSP70-2 gene (rs1061581) polymorphism and related risk factors.

The aim of the study is to evaluate the association of the HSP70-2 gene (rs1061581) A1267G polymorphism with AOM in children, as well as to assess the inheritance patterns of the disease and the AOM severity risks in the cohort.

Material and methods

Clinical material was collected at the Municipal Non-profit Enterprise «Multidisciplinary Hospital of Intensive Care» (Kitsman city) during 2023-2024. A total of 100 children with AOM participated in the prospective study. Of these, 95 children aged 7 to 18 years met the screening criteria, and their parents provided informed consent for participation. These children underwent a comprehensive evaluation, including anamnestic, clinical, laboratory, and instrumental examinations. The study complied with the Council of Europe Convention on Human Rights and Biomedicine principles, the basic provisions of GCP (1996), and the World Medical Association Declaration of Helsinki on the ethical principles of conducting scientific medical research involving human subjects. The study was approved by the Biomedical Ethics Commission of the Bukovinian State Medical University (BSMU). The clinical diagnosis of AOM and the AOM severity were established on the basis of the National Unified Clinical Protocol for Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care «Acute Otitis Media» approved by Order of the Ministry of Health of Ukraine (MOH) No. 688 dated April 9, 2021, and the corresponding Clinical Guidelines «Acute Otitis Media» (2021) [26; 27] and international recommendations on AOM [1; 6; 28]. When necessary, additional X-rays of the mastoid processes, paranasal sinuses, and chest were performed in two projections.

Children were stratified by age: 7-11 years (n=81) and 12-18 years (n=14); by AOM severity (severe – 45.26% (n=43), non-severe – 54.74% (n=52)); by the nature of mucosal inflammation (catarrhal – 52.63% (n=50), purulent – 47.37% (n=45)); by the condition of the eardrum (pre-perforative – 81.05% (n=77), perforative – 18.95% (n=18)); and by the allelic status of the HSP70-2 gene (rs1061581). The cohort comprised 34.74% (n=33) girls and 65.26% (n=62) boys. The control group included 50 healthy children matched by age and sex (girls/boys – 20/30), with no history of inflammatory diseases at any site during the preceding six months. The groups were comparable in terms of age ($p>0.05$).

Genotyping of the *HSP*70-2 gene was performed using quantitative Polymerase Chain Reaction (qPCR). The PCR products were separated by horizontal electrophoresis in agarose gel 3% stained with ethidium bromide (4 μl) and visualized by UV transluminator (Nyxtechnic, USA) using Vitran® computed-based program in the presence of a molecular mass ladder (100-1000 bp). The amplicon lengths were as follows: *GG*-genotype – 936 and 181 bp, *AG*-genotype – 1117, 936 and 181 bp, and *AA*-genotype – 1117 base pair (bp).

Statistical analysis was conducted using Statistica 7.0 (StatSoft Inc, USA) software and Excel® 2016™. Qualitative data (categorical variables) were analyzed using odds ratio (OR) with a 95% confidence interval (CI), employing the chi-square test (χ^2) (df=1) (for frequencies less than 5, Fisher's exact test was applied) and a multivariate logistic regression model. P values <0.05 were considered statistically significant.

The study was conducted as part of the comprehensive research project of the Family Medicine Department of BSMU, titled «Improvement of Diagnosis and Prediction of Hypertensive-Mediated Target Organ Damage and Symptom Control in Comorbid Pathology Considering Clinical-Metabolic and Molecular-Genetic Predictors» (State Registration Number 0124U002524, implementation period: 01.01.2024-31.12.2028).

Results and Discussion

The codominant model of AOM revealed no statistically significant differences in the overall distribution of relative frequencies of the HSP70-2 gene polymorphism (rs1061581) A1267G genotypes (Table 1) between patients and the control group ($\chi^2=5.17$; $p=0.075$). However, the GG genotype and G-allele were relatively more often registered in practically healthy individuals compared to children with AOM – by 17.16% ($\chi^2=3.94$; $p=0.047$) and 11.79% ($\chi^2=4.20$; $p=0.04$), respectively. The wild-type of the HSP70-2 gene (rs1061581) dominated in both groups, being 3.17 and 1.79 times more frequent ($p<0.001$). The mutant A-allele was more prevalent in the AOM patient group compared to healthy individuals by 11.79% ($p<0.05$).

The genotypes distribution of the HSP70-2 gene (rs1061581) 1267G>A polymorphism in the studied cohort generally conformed to the Hardy-Weinberg equilibrium ($\chi^2=1.36$; $p=0.243$) with a slight excess of heterozygosity observed across all groups (F= –0.21-/-0.18/; $p>0.05$).

Table1

Genotypes and alleles Distribution of the Heat Shock Protein gene HSP70-2 (rs1061581) A1267G polymorphism in the examined population

Genotypes and alleles, n (%)		Patients, n=95 (%)	Control, n=50 (%)	χ^2	p
HSP70-2 (A1267G), n (%)	AA	8 (8.42)	1 (2.0)	<1.0	0.164
	AG	52 (54.74)	22 (44.0)	1.51	0.219
	GG	35 (36.84)	27 (54.0)	3.94	0.047
χ^2;p		χ^2=5,17; p=0,075		-	-
HSP70-2 (A1267G), n (%)	G-allele	122 (64.21)	76 (76.0)	4.20	0.04
	A-allele	68 (35.79)	24 (24.0)		

Univariate analysis of risk models for the AOM development in the studied population, based on the A1267G polymorphism of the HSP70-2 gene (dominant, recessive, super-dominant and additive), is presented in Table 2. The dominant and additive models are reliable, the latter constructed using the Cochran-Armitage test for linear trends, according to which the AOM risk increases twofold in the presence of the mutant A-allele in the patient's genotype (OR=2.01; OR 95%CI: 1.01-4.06; p=0.05 and OR=2.01; OR 95%CI: 1.10-3.77; p=0.03), Akaike criterion (AC) 16.67 and 15.33, respectively. The most effective model in the studied population is the model with the lowest AC– this is an additive model in our case (AC=15.33), which determines the genetic predisposition to AOM in the surveyed population.

Table 2

Inheritance models of susceptibility to otitis media in children depending on the HSP70-2 gene polymorphism (rs1061581)

Genotypes	Patients, n=95 (%)	Control, n=50 (%)	OR [95% CI]	p	AC
Dominant model, df=1					
AG + AA	60 (63.16)	23 (46.0)	2.01 [1.01-4.06]	0.05	16.67
GG	35 (36.84)	27 (54.0)	1.00		
Recessive model, df=1					
AA	8 (8.42)	1 (2.0)	4.51 [0.79-84.83]	0.16	17.83
GG + AG	87 (91.58)	49 (98.0)	1.0		
Super-dominant model, df=2					
AG	52 (54.74)	22 (44.0)	1.54 [0.77-3.09]	0.22	19.08
GG + AA	43 (45.26)	28 (56.0)	1.0		
Additive model (Cochran-Armitage test for linear trends), df=1					
GG	35 (36.84)	27 (54.0)	1.0	0.03	15.33
2AA + AG	68 (71.58)	24 (48.0)	2.01 [1.10-3.77]		

Note. AC – Akaike coefficient; OR – Odds Ratio; CI-Confidence Interval; df – degrees of freedom.

The risk of AOM developing in the examined population considering the allelic status of the HSP70-2 gene (rs1061581), is presented in Table 3. The risk of AOM development in A-allele carriers increases nearly twofold (OR=1.76; OR 95%CI: 1.02-3.05; p=0.026) with the lowest the lowest risk observed in patients carrying the G-allele, especially in the homozygous state (GG-genotype) (OR=0.50; OR95%CI:0.25-0.99; p=0.035).

Table 3

Polymorphic variants of the HSP70-2 gene (rs1061581) as risk factors for acute otitis media in the population

Potential risk factors	OR	OR 95% CI	RR	RR 95% CI	p
AA-genotype (hypothetically)	4.51	0.55-37.10	4.21	0.54-32.72	0.119
GG-genotype	0.50	0.25-0.99	0.68	0.47-0.98	0.035
AG-genotype	1.54	0.77-3.07	1.24	0.87-1.79	0.146
A-allele	1.76	1.02-3.05	1.18	1.02-1.38	0.026
G-allele	0.57	0.33-0.68	0.84	0.73-0.98	

Note. RR – Risk Ratio; OR – Odds Ratio; CI-Confidence Interval; P – significance of differences.

The frequency of catarrhal AOM in children dominated in non-severe cases of the disease by 47.59%, especially at the age of 7-11 years, but in general, no significant differences were found (Fig. 1). At the same time, the purulent nature of ear discharge prevailed in severe AOM in prepubertal age children 7-11 years old (p=0.045).

Epidemiological analysis confirmed a probability increase of severe AOM more than 7 times for purulent discharge from the ear at the age of 7-11 years (OR=7.29; OR 95%CI: 1.44-37.01; p=0.045) with low chances of its development at the age of >12 years (OR=0.14; OR 95%CI: 0.03-0.70; p=0.019) (Fig. 2).

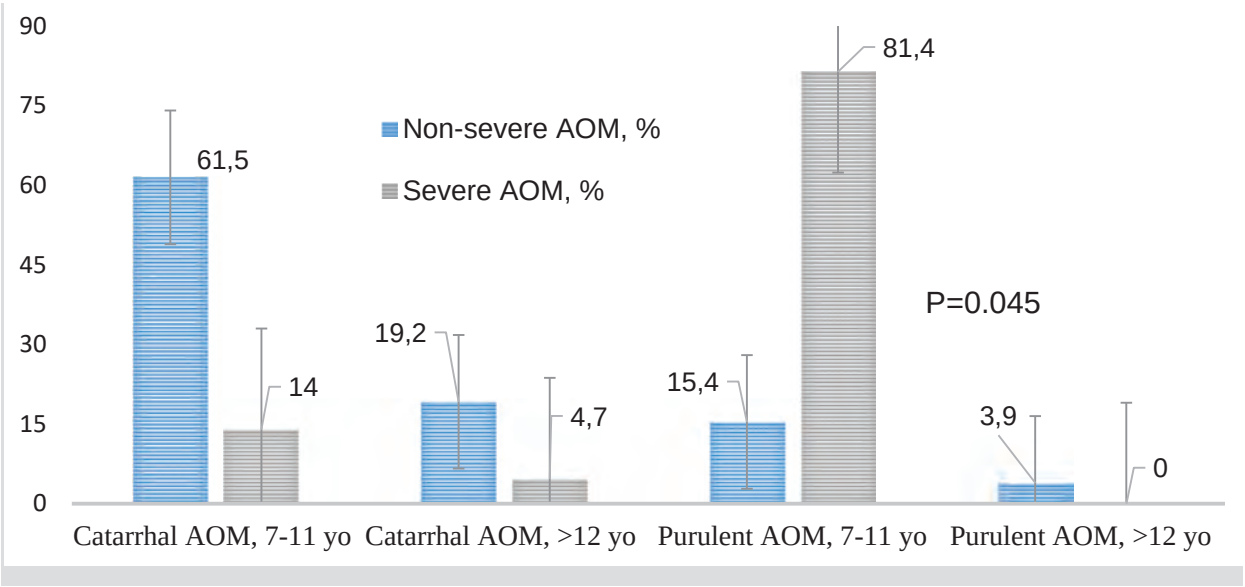

Figure 1. Severity of the Acute Otitis Media (AOM) in children and type of inflammatory process depending on age.

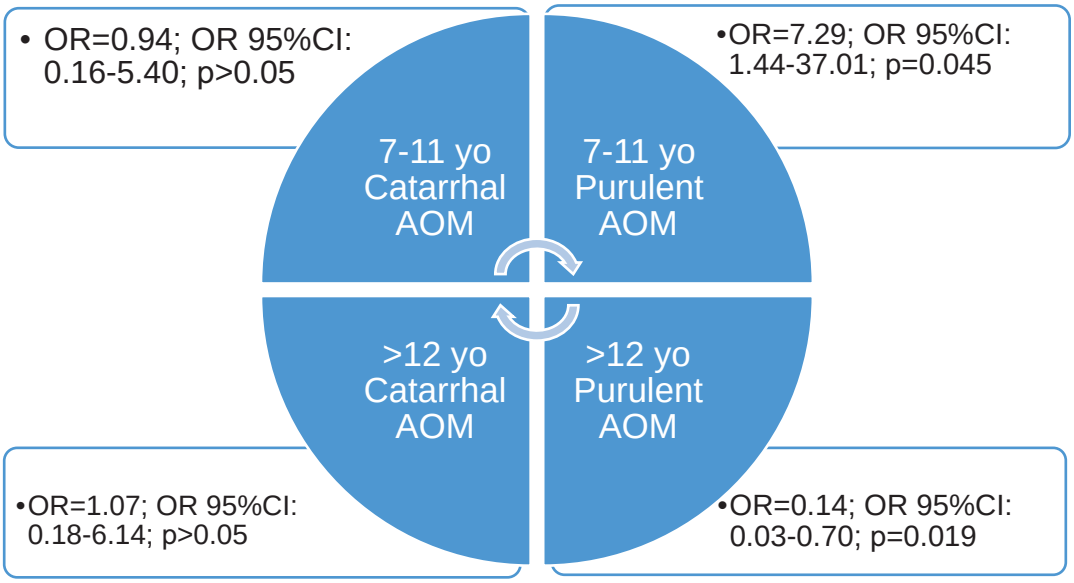

Figure 2. Predictors of severe acute otitis media (AOM) in children depending on the ear discharge and age.

Heat shock proteins, as molecular chaperone and proinflammatory stress marker, play relevant roles in the pathogenesis of inflammatory diseases. In research of Asea A. et al [29] HSP70 exhibits a high binding affinity for the plasma membrane, triggering a rapid intracellular calcium flux and activating nuclear factor-kappaB (NF-κB). This activation leads to the upregulation of pro-inflammatory cytokines, including interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF)-alpha in human monocytes. Notably, exogenous HSP70 initiates two distinct signal transduction pathways: one dependent on CD14 and intracellular calcium, promoting the production of IL-1β, IL-6, and TNF- α, while the other bypasses CD14 but depends on intracellular calcium, enhancing TNF- α production without affecting IL-1β or IL-6. These results highlight the role of CD14 as a co-receptor in HSP70-mediated signaling and reveal an additional extracellular regulatory function of HSP70 in monocytes, functioning both as a molecular chaperone and as a cytokine [29].

Muralidharan S et al. [30] suggested that cellular stress proteins – HSP70 and Heat Shock Transcription Factor protein1 (HSF1), play a key role in alcohol-induced inhibition of the TLR4/MyD88 signaling pathway. Their study demonstrated that alcohol exposure elevates HSF1 mRNA levels and its DNA-binding activity in human monocytes and murine macrophages. Additionally, alcohol upregulates the expression of the HSF1 target gene, HSP70, at both mRNA and protein levels in monocytes. Pre-exposure to moderate alcohol in vitro was shown to diminish lipopolysaccharide (LPS)-induced NF-κB promoter activity and the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), indicating a state of endotoxin tolerance. At later stages, HSP70 associates with

the NF-κB p50 subunit, further inhibiting NF-κB activity. Overexpression of HSP70 alone was sufficient to block LPS-induced NF-κB promoter activation, highlighting its role in alcohol-induced immunosuppression. These findings indicate that the alcohol-driven activation of HSF1 and subsequent induction of HSP70 are critical for the suppression of TLR4-MyD88 signaling and the development of alcohol-induced endotoxin tolerance [30].

In another study examining the mechanisms of Multiple Sclerosis (MS) lesion pathogenesis [22], two key neuroprotective functions of HSP70 were identified: first, as molecular chaperones, they assist in the proper folding of proteins and prevent their aggregation; second, they activate anti-apoptotic pathways, contributing to cell survival. Additionally, HSP70 facilitates the ubiquitination and degradation of misfolded proteins, ensuring proteostasis. Notably, HSP70 also exhibits cytokine-like activity by initiating pro-inflammatory signaling cascades in monocytes, leading to the increased expression of cytokines such as IL-1β, IL-6, and TNFα [29]. This dual role of HSP70 highlights its significance in both neuroprotection and immune modulation [22].

In our research we demonstrated that A-allele of HSP70-2 gene (rs1061581) is associated with AOM development and AOM severity. Consequently, we hypothesize that HSP70 in AOM condition may mediate an inhibition of TLR4-MyD88 signaling, initiating four distinct signal transduction pathways: one dependent on CD14 and intracellular calcium, promoting the production of IL-1β, IL-6, and TNF- α; another bypasses CD14 but depends on intracellular calcium, enhancing TNF-a production; thirdly, HSP70, as chaperones, assist in the proteins folding and prevent protein aggregation while facilitating the degradation of misfolded proteins; fourthly, HSP70 activates anti-apoptotic pathways, contributing to cell survival.

Conclusions. 1. The mutation of the heat shock protein gene HSP70-2 (rs1061581) in children with acute otitis media in Northern Bukovina is 35.79% (8.42% in homozygous condition). Binary logistic regression proved the significant probability of AOM development in A-allele carriers' children under the dominant and additive models (95%CI: 1.01-4.06; p=0.05 and 95%CI: 1.10-3.77; p=0.03).

2. Epidemiological analysis revealed an almost two-fold increased risk of AOM in children with A-allele of the HSP70-2 gene (rs1061581) (OR=1.76; OR 95%CI: 1.02-3.05; p=0.026). Furthermore, the risk of severe AOM increases more than sevenfold in cases of purulent ear discharge among children aged 7-11 years (OR=7.29; OR 95%CI: 1.44-37.01; p=0.045).

Prospects for further research include studying the transcriptional activity of the HSP70-2 gene (rs1061581) and molecular, anamnestic, and microsocial risk factors for AOM in children.

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References:

1. Danishyar A, Ashurst JV. Acute Otitis Media. 2023 Apr 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29262176.

2. Jamal A, Alsabea A, Tarakmeh M, Safar A. Etiology, Diagnosis, Complications, and Management of Acute Otitis Media in Children. Cureus. 2022;14(8): e28019. DOI: http://doi.org/10.7759/cureus.28019 PMID: 36134092; PMCID: PMC9471510.

3. World Health Organization. WHO mortality database. Interactive platform visualizing mortality data. Otitis media. Geneva: World Health Organization. 2020 Available from: https://platform.who.int/mortality/themes/theme-details/topics/indicator-groups/indicator-group-details/MDB/otitis-media

4. World Health Organization. Chronic suppurative otitis media: burden of illness and management options. Geneva: World Health Organization. 2004. 84 p. Available from: https://iris.who.int/handle/10665/42941

5. Gavrilovici C, Spoială EL, Miron IC, Stârcea IM, Haliţchi COI, Zetu IN, et al. Acute Otitis Media in Children-Challenges of Antibiotic Resistance in the Post-Vaccination Era. Microorganisms. 2022;10(8):1598. DOI: http://doi.org/10.3390/microorganisms10081598 PMID: 36014016; PMCID: PMC9413688.

6. Tuzger N, Milani GP, Folino F, Aldè M, Agostoni C, Torretta S, et al. Referrals for Recurrent Acute Otitis Media With and Without Spontaneous Tympanic Membrane Perforation Through COVID-19: A Cross-Sectional Comparative Study. Pediatr Infect Dis J. 2023;42(9): e356-7. DOI: http://doi.org/10.1097/INF.0000000000003970 PMCID: PMC10627387

7. Asea A, Rehli M, Kabingu E, Boch JA, Bare O, Auron PE, et al. Novel signal transduction pathway utilized by extracellular HSP70: role of toll-like receptor (TLR) 2 and TLR4. J Biol Chem. 2002;277(17):15028-34. DOI: http://doi.org/10.1074/jbc.M200497200 PMID: 11836257.

8. Sydorchuk LP, Syrota BS, Sydorchuk AR, Gerush OV, Muzyka NY, Sheremet MI, et al. Clinical markers of immune disorders in the pathogenesis of Escherichia coli enteritis. Arch Balk Med Union. 2019;54(1):89-96. DOI: http://doi.org/10.31688/ABMU.2019.54.1.12

9. Kampinga HH, Hageman J, Vos MJ, Kubota H, Tanguay RM, Bruford EA, et al. Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones. 2009;14(1):105-11. DOI: http://doi.org/10.1007/s12192-008-0068-7 PMID: 18663603; PMCID: PMC2673902

10. Sokolenko M, Sokolenko A, Sokolenko L. Influence of gene polymorphism, severity of clinical course of the disease and combination with comorbidities on cellular and general reactivity in patients with COVID-19. Med. Sci. of Ukr. 2024;20(2):45-2. DOI: https://doi.org/10.32345/2664-4738.2.2024.06

11. Tahara T, Shibata T, Okubo M, Ishizuka T, Kawamura T, Yamashita H, et al. Heat-shock protein 70-2 BB genotype is associated with reduced risks of the steroid-dependent and refractory phenotypes of ulcerative colitis. Biomed Rep. 2014;2(4):555-8. DOI: http://doi.org/10.3892/br.2014.28 PMID: 24944807; PMCID: PMC4051472.

12. Sydorchuk LP, Serdulets YI, Sydorchuk AR, Fediv OI, Havrysh LO, Teleki YM, et al. The polymorphism of matrilin-3 (rs77245812) and interleukin-10 (rs1800872) genes in osteoarthritis patients with arterial hypertension, obesity and type 2

diabetes mellitus. Arch Balk Med Union. 2017;52:422-9. Available from: https://umbalk.org/wp-content/uploads/2017/12/08.THE-POLYMORPHISM-OF-MATRILIN-3-RS77245812.pdf

13. David B, MacAry PA, Lehner PJ. Structure and function: heat shock proteins and adaptive immunity. J Immunol. 2007;179(4):2035-40. DOI: http://doi.org/10.4049/jimmunol.179.4.2035 PMID: 17675458.

14. Sherman M, Multhoff G. Review Heat shock proteins in cancer. Ann NY Acad Sci. 2007;1113:192-201. DOI: https://doi.org/10.1196/annals.1391.030

15. Fourie AM, Peterson PA, Yang Y. Characterization and regulation of the major histocompatibility complex-encoded proteins Hsp70-Hom and Hsp70-1/2. Cell Stress Chaperones. 2001;6(3):282-95. DOI: http://doi.org/10.1379/1466-1268(2001)006<0282:carotm>2.0.co;2 PMID: 11599570; PMCID: PMC434410.

16. Wang Y, Zhou F, Wu Y, Xu D, Li W, Liang S. The relationship between three heat shock protein 70 gene polymorphisms and susceptibility to lung cancer. Clin Chem Lab Med. 2010;48(11):1657-63. DOI: http://doi.org/10.1515/CCLM.2010.304 PMID: 20704535.

17. He M, Guo H, Yang X, Zhang X, Zhou L, Cheng L, et al. Functional SNPs in HSPA1A gene predict risk of coronary heart disease. PLoS One. 2009;4:48-51. DOI: http://doi.org/10.1371/journal.pone.0004851 PMID: 19333379; PMCID: PMC2659421.

18. Li JX, Tang BP, Sun HP, Feng M, Cheng ZH, Niu WQ. Interacting contribution of the five polymorphisms in three genes of Hsp70 family to essential hypertension in Uygur ethnicity. Cell Stress Chaperones. 2009;14(4):355-62. DOI: http://doi.org/10.1007/s12192-008-0089-2 PMID: 19085089; PMCID: PMC2728270.

19. Aquino-Gálvez A, González-Ávila G, Pérez-Rodríguez M, Partida-Rodríguez O, Nieves-Ramírez M, Piña-Ramírez I, et al. Analysis of heat shock protein 70 gene polymorphisms Mexican patients with idiopathic pulmonary fibrosis. BMC Pulm Med. 2015;15:129. DOI: http://doi.org/10.1186/s12890-015-0127-7 PMID: 26496868; PMCID: PMC4619986.

20. Ucisik-Akkaya E, Davis CF, Gorodezky C, Alaez C, Dorak MT. HLA complex-linked heat shock protein genes and childhood acute lymphoblastic leukemia susceptibility. Cell Stress Chaperones. 2010;15(5):475-85. DOI: http://doi.org/10.1007/s12192-009-0161-6 PMID: 20012387; PMCID: PMC3006629.

21. Zhang H, Jin T, Zhang G, Chen L, Zou W, Li QQ. Polymorphisms in heat-shock protein 70 genes are associated with coal workers' pneumoconiosis in southwestern China. In Vivo. 2011;25(2):251-7. PMID: 21471543.

22. Boiocchi C, Osera C, Monti MC, Ferraro OE, Govoni S, Cuccia M, Montomoli C, et al. Are Hsp70 protein expression and genetic polymorphism implicated in multiple sclerosis inflammation? Journal of Neuroimmunology 2014; 268: 84-8. DOI: http://doi.org/10.1016/j.jneuroim.2014.01.004 PMID: 24485944.

23. Zong J, Lin Y, Tian Q, Zhao X, Chu K, Jiang B, et al. HSPA1L rs1061581 polymorphism is associated with the risk of preeclampsia in Han Chinese women. Biosci Rep. 2020; 40(2): BSR20194307. DOI: http://doi.org/10.1042/BSR20194307 PMID: 32039449; PMCID: PMC7048671.

24. Partida-Rodríguez O, Torres J, Flores-Luna L, Camorlinga M, Nieves-Ramírez M, Lazcano E, et al. Polymorphisms in TNF and HSP-70 show a significant association with gastric cancer and duodenal ulcer. Int J Cancer. 2010;126(8):1861-8. DOI: http://doi.org/10.1002/ijc.24773 PMID: 19626584.

25. Mir KA, Pugazhendhi S, Paul MJ, Nair A, Ramakrishna BS. Heat-shock protein 70 gene polymorphism is associated with the severity of diabetic foot ulcer and the outcome of surgical treatment. Br J Surg. 2009;96(10):1205-9. DOI: http://doi.org/10.1002/bjs.6689 PMID: 19731315.

26. Ministerstvo okhorony zdorov'ia Ukrainy. Hostryi serednii otyt. Klinichna nastanova, zasnovana na dokazakh [Evidence-based clinical guideline, «Acute otitis media» [Internet]. Kyiv: MOZ Ukrainy; 2021. 94 p. [tsytovano 2025 Sich 10]. Dostupno: https://www.dec.gov.ua/wp-content/uploads/2021/04/2021_688_kn_gso.pdf

27. Ministerstvo okhorony zdorov'ia Ukrainy. Pro zatverdzhennia Unifikovanoho klinichnoho protokolu pervynnoi, vtorynnoi (spetsializovanoi) ta tretynnoi (vysokospetsializovanoi) medychnoi dopomohy «Hostryi serednii otyt [On Approval of the Unified Clinical Protocol for Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care «Acute Otitis Media»]. Nakaz MOZ Ukrainy № 688 vid 09.04.2021 r. [Internet]. Kyiv: MOZ Ukrainy; 2021. [tsytovano 2025 Sich 10]. Dostupno: https://zakon.rada.gov.ua/rada/show/v0688282-21#Text

28. Marchisio P, Galli L, Bortone B, Ciarcià M, Motisi MA, Novelli A, et al. Updated Guidelines for the Management of Acute Otitis Media in Children by the Italian Society of Pediatrics: Treatment. Pediatr Infect Dis J. 2019;38(12S Suppl): S10-21. DOI: http://doi.org/10.1097/INF.0000000000002452 PMID: 31876601.

29. Asea A, Kraeft SK, Kurt-Jones EA, Stevenson MA, Chen LB, Finberg RW, et al. HSP70 stimulates cytokine production through a CD14-dependant pathway, demonstrating its dual role as a chaperone and cytokine. Nat Med. 2000;6(4):435-42. DOI: http://doi.org/10.1038/74697 PMID: 10742151.

30. Muralidharan S, Ambade A, Fulham MA, Deshpande J, Catalano D, Mandrekar P. Moderate alcohol induces stress proteins HSF1 and hsp70 and inhibits proinflammatory cytokines resulting in endotoxin tolerance. J Immunol. 2014;193(4):1975-87. DOI: http://doi.org/10.4049/jimmunol.1303468 PMID: 25024384; PMCID: PMC4325985.

ГЕН БІЛКА ТЕПЛОВОГО ШОКУ 70-2 (RS1061581) АСОЦІЮЄ З РОЗВИТКОМ ГОСТРИХ СЕРЕДНІХ ОТИТІВ У ДІТЕЙ

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Резюме.

Гострий середній отит (ГСО) є одним із найпоширеніших дитячих захворювань у світі. Вражаючи мільйони дітей/підлітків щороку, ГСО створює серйозну проблему для охорони здоров'я. Незважаючи на те, що основні механізми розвитку ГСО відомі, молекулярні та генетичні особливості патогенезу захворювання потребують вивчення.

Мета дослідження. Встановити роль A1267G поліморфізму гена HSP70-2 (rs1061581) у розвитку ГСО у дітей, а також оцінити моделі успадкування захворювання та ризики тяжкості перебігу ГСО в когорті.

Матеріал та методи. У проспективному когортному дослідженні взяли участь 95 дітей із ГСО віком від 7 до 18 років. Серед обстежених дітей було 34,74% (n=33) дівчаток та 65,26% (n=62) хлопчиків. Дослідження проводили із дотриманням усіх вимог GCP, GLP, біомедичної етики щодо наукових медичних досліджень за участю людини. Інформовану згоду на участь у дослідженні підписали батьки кожної дитини. Учасників розподілили за віком (7-11 років (n=81) та 12-18 років (n=14)); тяжкістю ГСО (тяжкий – 45,26% (n=43), нетяжкий – 54,74% (n=52)), видом запалення слизових оболонок (катаральний – 52,63% (n=50), гнійний – 47,37% (n=). 45)). Контрольну групу склали 50 практично здорових дітей: 20 дівчаток (40,0%) і 30 хлопчиків (60,0%). За віком групи не відрізнялися (p>0,05). Поліморфізм гена HSP70-2 (rs1061581) досліджено методом якісної полімеразної ланцюгової реакції. Ризик оцінювали за відношенням ризику (RR) і шансів (OR) із 95% довірчим інтервалом (CI).

Результати. Мутація гена білка теплового шоку HSP70-2 (rs1061581) у дітей-мешканців Північної Буковини із ГСО зустрічається із частотою 35,79% (8,42% у гомозиготному стані), що на 11,79% частіше, ніж у практично здорових дітей (χ^2=4,20; p=0,04). Розподіл генотипів 1267G>A поліморфізму гена HSP70-2 (rs1061581) у когорті обстежених загалом відповідає закону популяційної рівноваги Hardy-Weinberg (χ^2=1,36; p=0,243) і за частотою алелей не відрізняється від середнього показника для європеоїдних популяцій (P_A=0,24-0,36; P_G=0,64-0,76). Бінарна логістична регресія встановила ймовірність розвитку ГСО у дітей-носіїв А-алеля в рамках домінантної та адитивної моделей (OR=2,01; 95%CI: 1,01-4,06; p=0,05 та OR=2,01; 95%CI: 1,10-3,77; p=0,03) із найнижчим коефіцієнтом позавибіркового передбачення Акайке (КА=16,67 і 15,33).

Епідеміологічний аналіз підтвердив збільшення ризику появи ГСО у дітей-носіїв А-алеля гена HSP70-2 (rs1061581) майже удвічі (OR=1,76; OR 95%CI: 1,02-3,05; p=0,026) за найнижчих шансів у власників G-алеля, особливо у гомозиготному стані (OR=0,50; OR95%CI: 0,25-0,99; p=0,035). Окрім того, ймовірність тяжкого ГСО зростає у понад 7 разів за гнійних виділень із вуха у віці 7-11 років (OR=7,29; OR 95%CI: 1,44-37,01; p=0,045) із низькими шансами на його розвиток в пубертатному віці (12-18 років) (OR=0,14; OR 95%CI: 0,03-0,70; p=0,019).

Висновки. А-алель гена HSP70-2 (rs1061581) збільшує ризик ГСО майже удвічі в обстеженій когорті дітей. Ризик важкого перебігу ГСО зростає більш ніж у 7 разів за гнійних виділень із вуха у віці 7-11 років.

Ключові слова: гострий середній отит; ген HSP70-2 (rs1061581); діти; білок теплового шоку; ризики; запалення; тяжкість захворювання.

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