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GEORGIAN MEDICAL NEWS


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სტი ქმედით, ქმედით ძალიან ბევრი და ძალიან გამოქვეყნილ ტექსტი (ქმედ 
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THE PREVALENCE OF C3953T IL1β GENE AND G308A TNFA GENE POLYMORPHIC VARIANTS IN THE PATIENTS WITH DIFFERENT TYPES OF ENCEPHALOPATHIES

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Abstract.

Introduction: It is essential to study disorders of the immune system in chronic encephalopathies of various genesis, considering that the mechanisms of brain damage remain unknown in their molecular basis. Among numerous inflammatory mediators, cytokines are particular in regulating immunological interactions. Many factors, including the genetic ones, determine these pro-inflammatory proteins’ activity.

Aim: The aim of study was to study the prevalence of IL1β C3953T gene polymorphism and TNFα G308A gene polymorphism in patients with chronic traumatic encephalopathy (CTE), microvascular ischemic disease of the brain (or cerebral small vessel disease, (SVD)), chronic alcohol-induced encephalopathy (AIE) and postinfectious encephalopathy (PIE), and to evaluate the impact of a particular genotype presence on the occurrence and/or progression of encephalopathy.

Materials and methods: The molecular genetic study of polymorphic variants - C3953T of the IL1β gene and G308A of the TNFα gene was applied for 96 patients with encephalopathies of various genesis (CTE n=26, CAIE n=26, SVD n=18, and PIE n=26). The patients were undergoing treatment in the neurological departments of the Communal Non-commercial Enterprise “Ternopil Regional Clinical Psychoneurological Hospital” of Ternopil Regional Council (Ternopil, Ukraine) during 2021–2022. The control group consisted of 12 healthy persons, who were representative in terms of age and sex. Statistical processing of the results was carried out using the STATISTICA 10.0 software package.

Results and discussion: The frequency distribution analysis of the genotypes of the polymorphic variant C3953T of the IL1β gene and G308A of the TNFα gene was applied for 96 patients with encephalopathies of various genesis (CTE n=26, CAIE n=26, SVD n=18, and PIE n=26). The patients were undergoing treatment in the neurological departments of the Communal Non-commercial Enterprise “Ternopil Regional Clinical Psychoneurological Hospital” of Ternopil Regional Council (Ternopil, Ukraine) during 2021–2022. The control group consisted of 12 healthy persons, who were representative in terms of age and sex. Statistical processing of the results was carried out using the STATISTICA 10.0 software package.

Conclusions: For the first time in the Ukrainian population, an analysis of the frequency distribution of the genotypes of the polymorphic variant C3953T of the IL1β gene and G308A of the TNFα gene in patients with chronic encephalopathies of various genesis was performed. Statistically, significant differences were found only in patients with PIE compared to healthy individuals. At the same time, the presence of the C/T genotype of the IL1β gene increases the risk of encephalopathy and/or progression of PIE by 8.0 times, and the presence of the G/A genotype of the TNFα gene by 9.4 times, which indicates the feasibility of including the corresponding single-nucleotide polymorphisms in the genetic panel of the study patients with PIE.

Key words. Encephalopathy, C3953T IL1β gene, G308A TNFα gene, gene polymorphism.

Introduction.

Neurological disorders are a significant and increasing global health challenge that would significantly impair cognitive-motor function. Globally, in 2019, there were nearly 10 million deaths and 349 million disability-adjusted life years (DALYs) due to neurological disorders [1,2]. In neurological pathology, encephalopathies remain the most relevant and socially significant due to the steady increase in morbidity, the development of pronounced neuropsychological disorders, the negative impact on the quality of life, and the early disability of patients [3]. Encephalopathy (EP) is a broad term that encompasses a wide range of presentations and aetiologies. The term is often used heterogeneously, and conformity to strict definitions and confirmation of the pathophysiology can be lacking [4]. Given the fact that the pathogenetic mechanisms of brain damage, in their molecular basis, remain unknown, it is essential to study disorders of the immune system in encephalopathies of various genesis. There is data that the mechanisms of immunological response affect the course of the disease [5].

Due to the presence of the blood-brain barrier (BBB), the absence of a classic lymphatic system, and the limited penetration of peripheral immunocompetent cells into its parenchyma, the brain has traditionally been considered an immune-privileged organ. However, nonspecific, and specific immune response elements are readily organized in the central nervous system upon the action of various pathogens, autoantigens, or brain tissue damage of multiple etiologies. Astrocytes, microglia, neurons, endothelial cells of the BBB, and blood cells that
penetrate the brain parenchyma produce pro-inflammatory and anti-inflammatory molecules. Among the numerous mediators of inflammation, a unique role in regulating immunological interactions is played by cytokines, which induce or suppress their synthesis, the synthesis of other cytokines and their receptors, participating in the formation of a cytokine network [6-8].

Many factors, including genetic ones, determine the activity of the cytokine network. Cytokine genes have an extremely high degree of polymorphism, and the number of polymorphic regions in one gene can reach several dozen and be localized both in the coding regions of the gene - exons, as well as in non-coding introns and promoter regions of the gene [9].

The activity of the immune response is related to the polymorphism of genes encoding cytokines. In other words, the presence of allelic polymorphism ensures the diversity of individuals in the degree of cytokine production during the formation of cellular reactions [10-12]. An allelic pair of genes can be homozygous or heterozygous. Each gene has two or more allelic variants, with the most common allele occurring in the population at a frequency of ≤95%. Alleles can exist in two alternative states—wild and mutant. A wild-type allele is a typical (“normal”) form of a gene, usually the most common phenotype in a natural population; in contrast, a mutant allele is the result of a mutation, a nucleotide substitution [13].

**The aim** was to study the prevalence of IL1β C3953T gene polymorphism and TNFα G308A gene polymorphism in patients with CTE, SVD, CAIE, and PIE and to assess the influence of the presence of a particular genotype of the studied genes on the occurrence and/or progression of encephalopathy.

**Materials and methods.**

96 patients with encephalopathies of various genesis were examined. All the patients were undergoing treatment in the neurological departments of the Communal Non-commercial Enterprise “Ternopil Regional Clinical Psychoneurological Hospital” of Ternopil Regional Council (Ternopil, Ukraine) during 2021–2022. The formation of groups of examined patients was based on the genesis of encephalopathy; in particular, the distribution by type of encephalopathies was as follows: chronic traumatic encephalopathy (CTE) – 26, chronic alcohol-induced encephalopathy (AIE) – 26, microvascular ischemic disease of the brain (or cerebral small vessel disease, (SVD)) – 18 and post-infectious encephalopathy (PIE) – 26. The control group (CG) consisted of 12 people, representative in terms of age and sex.

Considering the fact that currently there is no unified classification of encephalopathies and their stages, which would take into account the genesis and clinic of each type, the verification of various types of encephalopathies was carried out according to the criteria proposed by several authors [2-4].

Numerous factors, in particular, determine the course of each of the studied subtypes of encephalopathies, the immediate cause of encephalopathy, the influence of this cause on the development and progression of brain tissue damage and clinical manifestations, respectively, as well as the effect of concomitant diseases and the degree of their compensation. Each type of encephalopathy, depending on the severity and course of the disease, is characterized by a particular spectrum of neurological symptoms: behavior disorders, apathy, changes in memory and attention, decline in cognitive functions up to dementia, extrapyramidal disorders, pyramidal insufficiency, moderate neurological deficit.

Patient inclusion criteria were the following: age from 18 to 75 years; compliance with diagnosis criteria; availability of the patient's informed consent. Exclusion criteria: the presence of oncopathology; concomitant pathology in the stage of decompensation; use of psychoactive substances, the presence of other diseases that could be the cause of psychoneurological disorders, behavioral and mental disorders.

The performed study is a single-moment clinical study of the "case-control" type. The study protocol included screening of patients to determine compliance with inclusion and exclusion criteria, carrying out laboratory determinations, genetic research, and statistical analysis of the obtained data. All patients were informed about the purpose of the clinical study and gave written informed consent for their participation in it. Confidentiality about the patient's identity and state of health was preserved. The patient's informed consent form, examination card, and all stages of the research were approved by the bioethics commission of the Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine.

Molecular genetic study of the polymorphic variant C3953T of the IL1β gene and G308A of the TNFα gene. Its first stage was isolating DNA from whole peripheral blood on a paper blank using the commercial kit “Quick-DNA Miniprep Plus Kit” (Zymo Research, USA) according to the instructions. Molecular and genetic differentiation of the studied gene variants was carried out by the methods of allele-specific PCR or RFLP PCR (restriction fragment length polymorphism) by standard operational protocols developed in the molecular genetics laboratory of the SI “RCMD of Public Health Ministry of Ukraine”.

Electrophoretic distribution was carried out in the System for horizontal electrophoresis multi–Sub Midi (Cleaver Scientific, Great Britain). The size of amplified and restriction fragments was estimated by comparison with the molecular weight marker Gene Ruler DNA Ladder (Thermo Scientific, USA) in an ethidium bromide-stained 3% agarose gel (Cleaver Scientific, UK). In the visualization process, the formed fragments for each sample were evaluated, and photofixation of the obtained images was carried out. Samples were genotyped according to facility-approved SOPs by considering the molecular weight of the restriction/amplified fragments compared to the molecular weight of the corresponding positive control samples (Table 1).

**Table 1. Molecular weight of restriction/amplified fragments.**

<table>
<thead>
<tr>
<th>Gene and polymorphism, rs</th>
<th>The size of the restriction/amplified fragments and the corresponding genotype</th>
</tr>
</thead>
</table>
Statistical analysis.

The Hardy-Weinberg law was used to assess the correspondence between the genotypes of the selected sample and the general population. Comparison of observed frequencies and expected frequencies (Pearson Chi-Square, χ²), calculated using Pearson's formula: $p^2 + 2pq + q^2 = 1$ (Hardy-Weinberg equilibrium), was carried out using Pearson's χ²-square. When obtaining values of the reliability coefficient $p>0.05$, we accepted the "null" hypothesis about the equality of the samples, that is, the correspondence between the selected model and the general population. Comparative analysis of frequency tables was performed using Pearson Chi-Square ($χ^2$) and Fisher exact p, two-tailed (in those cases when the values of expected frequencies (expected frequencies) of individual indicators did not exceed 5). To assess the influence of the factor (the presence of a particular gene genotype) on the investigated feature (occurrence and progression of the disease), the odds ratio (OR) and its 95% confidence interval (95% CI) were calculated. The influence was considered statistically probable at $p<0.05$ for the OR.

Results.

Analysis of the frequency distribution of IL1β C3953T gene genotypes according to the Hardy-Weinberg law in patients with CTE, SVD, CAIE, and PIE and assessment of compliance with population balance was performed in all observation groups and the control group. It was established that the frequency of the genotype responsible for the T/T polymorphism of the IL1β gene both in patients with various types of encephalopathies and in the control, group did not deviate significantly from the Hardy-Weinberg equilibrium ($p>0.05$) (Table 2).

Analysis of the frequency distribution of TNFα G308A gene genotypes according to the Hardy-Weinberg law in patients with the studied types of encephalopathies and assessment of compliance with population balance was carried out in all observation groups and the control group. It was established that the frequency of the genotype responsible for the G/A polymorphism of the TNFα gene both in patients with various types of encephalopathies and in the control group did not significantly deviate from the Hardy-Weinberg equilibrium ($p>0.05$) (Table 3).

Analyzing the frequency distribution of IL1β gene genotypes in patients with the studied types of encephalopathies and the control group, it was found that the C/C genotype prevailed in patients with CTE, SVD, CAIE, and in the control group, while the T/T genotype prevailed in patients with PIE (Table 4). In addition, T/T genotype carriers were found only among patients with PIE. Comparing the distribution of genotypes of the IL1β gene in patients with the studied types of encephalopathies and controls, statistically significant differences were found only in patients with PIE, in whom the distribution of genotype frequencies according to the polymorphic variant of the IL1β gene was as follows: 26.92% of people were carriers of the C/C genotype, 61.54% – C/T genotype and 11.54% – T/T genotype. In addition, in the group of patients with PIE, IL1β gene genotype frequency distribution probably differed from the data of patients with CTE, SVD, and PIE ($q^2=28.64; p<0.001$).

The results of the frequency distribution of TNFα gene genotypes showed that the G/G genotype predominated in patients with CTE, SVD, CAIE, and in the control group, while in patients with PIE, the frequency distribution of G/G and G/A genotypes was even (Table 3). In patients with CTE, CAIE, PIE, and in controls, the A/A genotype of the TNFα gene was not detected. Comparing the distribution of genotypes of the TNFα gene in patients with the studied types of encephalopathies and controls, statistically significant differences were found only in patients with PIE, in whom the distribution of genotype frequencies according to the polymorphic variant of the TNFα gene was as follows: 53.85% of people were carriers of the G/G genotype, 46.15% – G/A genotype and 0.0% – A/A genotype. At the same time, in the group of patients with CAIE, the frequency distribution of TNFα gene genotypes probably differed from the data of patients with SVD and PIE ($q^2=24.91; p=0.002$).

Analyzing the odds ratio and its confidence interval for the genotypes of the IL1β gene in patients with the studied types of encephalopathies, it was established that there is a statistically significant relationship between the carrier of the CT and CC genotypes and the risk of encephalopathy in patients with PIE (Table 5). Thus, the presence of the CT genotype increases the risk of encephalopathy in this cohort of patients by 8.0 times. In contrast, the presence of the CC genotype of the IL1β gene polymorphism has protective properties regarding the risk of encephalopathy in patients with PIE.

Analyzing the odds ratio and its confidence interval for the genotypes of the TNFα gene in patients with the studied types of encephalopathies, it was established that there is a statistically significant relationship between the carrier of the GA and GG genotypes and the risk of encephalopathy in patients with PIE (Table 6). Thus, the presence of the GA genotype increases the risk of encephalopathy in this cohort of patients by more than 9 times. In contrast, the presence of the GG genotype has protective properties regarding the risk of encephalopathy in patients with PIE. In addition, the protective properties of the GG genotype regarding the risk of encephalopathy in patients with SVD were revealed.

Discussion.

Among the numerous mediators of inflammation, cytokines play a special role in the regulation of immunological interactions, the role of which has also been proven in neurodamage. Interleukin one beta (IL1β) is the most important member of the IL-1 family. It is produced by numerous cell types, including brain parenchyma, neurons, and astrocytes after brain ischemic insult and its levels are increased after trauma. IL1β is also considered an important mediator of inflammation after cerebrovascular ischemia [14]. There is evidence that IL1β, released in the brain, contributes to the production of NO, and its levels in the brain reflect the degree of hypoxic-ischemic damage [15,16].

The gene encoding IL1β is mapped to chromosome 2 (2q14). In the region of this gene, 135 single-nucleotide substitutions were found, and the +3953C/T polymorphism is located in exon 5 of this gene, causing the substitution of cytosine (C) for thymine (T) at position +3953 of the nucleotide sequence. Analyzing the frequency distribution of the genotypes of the C3953T polymorphic variant of the IL1β gene in patients with
### Table 2. IL1β gene polymorphism according to the Hardy-Weinberg law in patients with different types of encephalopathies.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CTE</th>
<th>SVD</th>
<th>CAIE</th>
<th>PIE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>expected</td>
<td>Available</td>
<td>expected</td>
<td>available</td>
<td>expected</td>
</tr>
<tr>
<td>Homozygotes that occur frequently</td>
<td>C/C</td>
<td>16,96</td>
<td>16</td>
<td>14,22</td>
<td>14</td>
</tr>
<tr>
<td>Heterozygotes</td>
<td>C/T</td>
<td>8,08</td>
<td>10</td>
<td>3,56</td>
<td>4</td>
</tr>
<tr>
<td>Homozygotes, which are rare</td>
<td>T/T</td>
<td>0,96</td>
<td>0</td>
<td>0,22</td>
<td>0</td>
</tr>
<tr>
<td>( \chi^2, p )</td>
<td>( \chi^2=1,47; p&gt;0,05 )</td>
<td>( \chi^2=0,28; p&gt;0,05 )</td>
<td>( \chi^2=0,18; p&gt;0,05 )</td>
<td>( \chi^2=1,77; p&gt;0,05 )</td>
<td>( \chi^2=0,10; p&gt;0,05 )</td>
</tr>
</tbody>
</table>

Note. * ‒ statistically significant result.

### Table 3. Polymorphism of the TNFα gene according to the Hardy-Weinberg law in patients with various types of encephalopathies.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CTE</th>
<th>SVD</th>
<th>CAIE</th>
<th>PIE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>expected</td>
<td>available</td>
<td>expected</td>
<td>available</td>
<td>expected</td>
</tr>
<tr>
<td>Homozygotes that occur frequently</td>
<td>G/G</td>
<td>18,62</td>
<td>18</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Heterozygotes</td>
<td>G/A</td>
<td>6,77</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Homozygotes, which are rare</td>
<td>A/A</td>
<td>0,62</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>( \chi^2, p )</td>
<td>( \chi^2=0,86; p&gt;0,05 )</td>
<td>( \chi^2=1,13; p&gt;0,05 )</td>
<td>( \chi^2=0,18; p&gt;0,05 )</td>
<td>( \chi^2=2,34; p&gt;0,05 )</td>
<td>( \chi^2=0,02; p&gt;0,05 )</td>
</tr>
</tbody>
</table>

Note. * ‒ statistically significant result.

### Table 4. IL1β and TNFα gene polymorphisms in patients with different types of encephalopathies.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CTE</th>
<th>SVD</th>
<th>CAIE</th>
<th>PIE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>CTE</td>
<td>16</td>
<td>61,54</td>
<td>77,78</td>
<td>84,62</td>
<td>26,92</td>
</tr>
<tr>
<td>SVD</td>
<td>10</td>
<td>38,46</td>
<td>22,22</td>
<td>15,38</td>
<td>61,54</td>
</tr>
<tr>
<td>CAIE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PIE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( \chi^2, p )</td>
<td>( \chi^2=1,80; p=0,179 )</td>
<td>( \chi^2=0,14; p=0,709 )</td>
<td>( \chi^2=0,01; p=0,920 )</td>
<td>( \chi^2=10,71; p=0,005^{*} )</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Odds ratios for IL1β genotypes in patients with different types of encephalopathies.**

<table>
<thead>
<tr>
<th>Type of encephalopathy</th>
<th>IL1β gene polymorphism</th>
<th>C/T</th>
<th>T/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/CT</td>
<td>0,32</td>
<td>0,56–17,30</td>
<td>0,47</td>
</tr>
<tr>
<td>SVD</td>
<td>0,70</td>
<td>0,11–4,59</td>
<td>1,43</td>
</tr>
<tr>
<td>CAIE</td>
<td>1,10</td>
<td>0,17–7,03</td>
<td>0,91</td>
</tr>
<tr>
<td>PIE</td>
<td>0,07^{*}</td>
<td>0,01–0,42</td>
<td>8,00^{*}</td>
</tr>
</tbody>
</table>

Note. * ‒ statistically significant result.
CTE, SVD, CAIE and PIE compared to individuals of the control group, statistically significant differences were found only in patients with PIE, among whom the most carriers of the C/T genotype and the least of the T/T genotype were found. According to the data obtained by Aguet F. and coauthors (2020), the expression of IL-1β is highest in TT genotype and lowest in CC [17]. Licastro F. et al. investigated whether IL-1β polymorphisms affected neuro-pathological features and clinical status of Alzheimer's disease (AD) patients with autopsy confirmed diagnosis. AD patients (n=133) were genotyped for the polymorphic regions in the apolipoprotein E ε (APOE ε) and interleukin-1β (IL-1β) genes. The IL-1β +3953 polymorphism influenced survival in AD patients and those with the TT genotype and without the APOE ε4 allele showed the shortest cumulative survival [18].

TNF-α is a pro-inflammatory cytokine with a wide range of biological functions, in particular, it induces the synthesis of macrophages and dendritic cells, pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNFα activate cells of innate immunity. In addition, TNFα increases the cytotoxic properties of NK cells and the production of IFNγ, which activates various cells of innate immunity and induces the differentiation of T cells according to the Th1 pathway. The human TNF-α gene is located on chromosome 6p21.1–21.3 within the highly polymorphic region of the major histocompatibility complex [19]. The TNFα G308A polymorphism – a single nucleotide polymorphism involving guanine to adenine substitution at position 308 in the promoter region of the TNFα gene. This polymorphism is functional, that is, it causes changes in the level of TNF-α production [20].

Analyzing the frequency distribution of the genotypes of the polymorphic variant G308A of the TNFα gene showed that in patients with CTE, SVD, CAIE, PIE compared to the control group, statistically significant differences were found only in patients with PIE, among whom no carriers of the A/A genotype were found, and the number of genotype carriers G/G and G/A was parity. Wang T. conducted a meta-analysis that showed that TNF-alpha G308A polymorphism may be associated with the increased risk of AD in Chinese and decreased risk of AD in northern European populations [21].

Our results regarding statistically significant differences in the frequency distribution of genotypes of polymorphic variants of the studied proinflammatory cytokine genes only in patients with PIE can be related to neuroinflammation, which is a common feature of encephalopathies associated with infectious diseases. In the brain, cytokines are able to activate glial cells, modulate the metabolism of neurotransmitters and lead to neurotoxic cascades [22]. After exposure to proinflammatory stimuli, microglia undergo morphological and functional changes and organize an immune response in the CNS. The proinflammatory environment also leads to several pathological changes in astroglia. This reactive astrogliosis is characterized by hypertrophy, a modified secretome, and increased expression of intermediate filament proteins, especially glial fibrillary acidic protein, and vimentin [23].

### Table 6. Odds ratios for TNFα genotypes in patients with different types of encephalopathies.

<table>
<thead>
<tr>
<th>Type of encephalopathy</th>
<th>TNFα gene polymorphism</th>
<th>OR</th>
<th>95 % CI</th>
<th>OR</th>
<th>95 % CI</th>
<th>OR</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>0.20</td>
<td>0.02−1.86</td>
<td>4.89</td>
<td>0.54−44.57</td>
<td>0.47</td>
<td>0.01−25.18</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>0.09*</td>
<td>0.01−0.86</td>
<td>5.50</td>
<td>0.57−53.22</td>
<td>5.65</td>
<td>0.27−119.85</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>0.50</td>
<td>0.05−5.03</td>
<td>2.00</td>
<td>0.20−20.10</td>
<td>0.47</td>
<td>0.01−25.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.11*</td>
<td>0.01−0.95</td>
<td>9.43*</td>
<td>1.06−84.04</td>
<td>0.47</td>
<td>0.01−25.18</td>
</tr>
</tbody>
</table>

Note. * – statistically significant result.

### Conclusion.

1. Analyzing the frequency distribution of genotypes of the C3953T polymorphic variant of the IL1β gene in patients with CTE, SVD, CAIE, PIE relative to healthy individuals, statistically significant differences were found only in patients with PIE (26.92% vs. 83.33% - carriers of the C/C genotype, 61.54% versus 16.67% – carriers of the C/T genotype and 11.54% versus 0% – carriers of the T/T genotype). In addition, in the group of patients with PIE, the distribution of genotype frequencies probably differs from the data of patients with CTE, SVD, and PIE (χ²=28.64; p<0.001).

2. Analyzing the frequency distribution of genotypes of the polymorphic variant G308A of the TNFα gene showed that in patients with CTE, SVD, CAIE, PIE compared to healthy individuals, statistically significant differences were found only in patients with PIE (53.85% vs. 91.67% - carriers of the G/G genotype, 46.15% versus 8.33% – carriers of the G/A genotype and 0.0% versus 0.0% – carriers of the A/A genotype). At the same time, in the group of patients with CAIE, the distribution of genotype frequencies probably differed from the data of patients with SVD and PIE (χ²=24.91; p=0.002).

3. Analyzing the odds ratio and its confidence interval for the genotypes of polymorphic variants C3953T of the IL1β gene and G308A of the TNFα gene in patients with CTE, SVD, CAIE, and PIE, it was established that the presence of the C/T genotype of the IL1β gene increases the risk of occurrence and/or progression of encephalopathy in patients with PIE by 8.0 times, and the presence of the G/A genotype of the TNFα gene increases the risk of occurrence and/or progression of encephalopathy in patients with PIE by 9.4 times, which indicates the feasibility of including the corresponding single nucleotide polymorphisms of the IL1β and TNFα genes in the genetic panel of patients with PIE to prescribe adequate therapy to prevent disease progression.

### REFERENCES