

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (340-341) Июль-Август 2023

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press.
Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Hasanov N.H, Istomin A.G, Istomin D.A. MATHEMATICAL JUSTIFICATION OF THE CHOICE OF RODS FOR EXTERNAL FIXATION DEVICES FOR POLYSTRUCTURAL PELVIC INJURIES.....	6-13
B. Todorova, I. Bitoska, A. Muca, O.Georgieva Janev, T. Milenkovic. A RARE CASE OF A PATIENT WITH HYPERTHYROIDISM AFTER HYPOTHYROIDISM.....	14-16
Satyaapir Sahu, Shabir Ahmad Shah, Supriti, Apurva Kumar R Joshi, Devanshu Patel J, Asha Yadav. THE GUT-BRAIN AXIS: IMPLICATIONS FOR NEUROLOGICAL DISORDERS, MENTAL HEALTH, AND IMMUNE FUNCTION..	17-24
Sara Mohammed Oudah Al-Saedi, Israa Hussein Hamzah. THE ROLE GENE EXPRESSION OF PD-1 AND PD-L1 IN NEWELY DIAGNOSED AND TREATED PATIENTS WITH ACUTE MYELOIDLEUKEMIA.....	25-29
Stepanyan L, Lalayan G, Avetisyan A. AN INVESTIGATION OF PSYCHOLOGICAL AND PHYSIOLOGICAL FACTORS AFFECTING PERFORMANCE IN ADOLESCENT JUDOKAS.....	30-36
Takuma Hayashi, Nobuo Yaegashi, Ikuo Konishi. EFFECT OF RBD MUTATIONS IN SPIKE GLYCOPROTEIN OF SARS-COV-2 ON NEUTRALIZING IGG AFFINITY.....	37-46
Yahya Qasem Mohammed Taher, Muna Muneer Ahmed, Hakki Mohammed Majdal. A CLINICO-EPIDEMIOLOGICAL STUDY OF MULTIPLE SCLEROSIS IN MOSUL CITY, IRAQ.....	47-52
Simona Kordeva, Georgi Tchernev. THIN MELANOMA ARISING IN NEVUS SPILUS: DERMATOSURGICAL APPROACH WITH FAVOURABLE OUTCOME.....	53-55
Buthaina H. Al-Sabawi, H. S. Sadoon. HISTOCHEMICAL CHANGES OF THE PULMONARY HYDATID CYSTS IN SHEEP INFECTED WITH CYSTIC ECHINOCOCCOSIS.....	56-60
Rocco De Vitis, Marco Passiatore, Vitale Cilli, Massimo Apicella, Giuseppe Taccardo. SARS-COV-2 INFECTION AND INVOLVEMENT OF PERIPHERAL NERVOUS SYSTEM: A CASE SERIES OF CARPAL TUNNEL SYNDROME AGGRAVATION OR NEW ONSET WITH COVID-19 DISEASE AND A REVIEW OF LITERATURE.....	61-66
L. Dzyak, K. Miziakina. NEURAL PROTEINS AS MARKERS FOR DIAGNOSING STRUCTURAL DAMAGE TO BRAIN MATTER IN POST-TRAUMATIC NEUROCOGNITIVE DISORDERS.....	67-70
Hiba M. Al-Khuzayy, Yasir H. Al-Juraisy, Ali H. Alwan. PURIFICATION, CHARACTERIZATION, AND IN VITRO ANTITUMOR ACTIVITY OF A NOVEL GLUCAN FROM PHOENIX DACTYLIFERA L. FRUITS.....	71-75
Natalia Stepaniuk, Oleh Piniashko, Olesia Poshvyak, Tetiana Bessarab, Natalia Hudz, Irina Gavriluk. MANAGEMENT OF RISKS OF ADVERSE DRUG REACTIONS ACCORDING TO ADR REPORT FORM DATA FROM LVIV REGION HEALTHCARE FACILITIES IN 2022.....	76-80
Ghazwan M. Radhi, Nihad N. Hilal, Mohammed M. Abdul-Aziz. TESTOSTERONE AND SERUM ZINC LEVELS IN MEN WITH BENIGN PROSTATIC HYPERPLASIA.....	81-86
Zora Khan, Deepthi Krishna, Surya Shekhar Daga, Nitin Kumar Rastogih, Rekha MM, Komal Patel. ADVANCEMENTS IN MINIMALLY INVASIVE SURGERY: A COMPREHENSIVE ANALYSIS OF ROBOTIC SURGERY, ENDOSCOPIC TECHNIQUES, AND NATURAL ORIFICE TRANSLUMENAL ENDOSCOPIC SURGERY (NOTES).....	87-92
Aditi Jane, Manoj Rameshachandra Vyas, Anil Kumar, Anurag Verma, Giresha AS, Devanshu Patel J. LIVER FIBROSIS: PATHOPHYSIOLOGY, DIAGNOSIS, AND EMERGING THERAPEUTIC TARGETS FOR A COMMON COMPLICATION OF CHRONIC LIVER DISEASES.....	93-100
Dilip Kumar Pati, Abhishek Roy, Mayur Porwal, Beemkumar N, Geetika Patel M, Sunita Bhatt. INNOVATIONS IN ARTIFICIAL ORGANS AND TISSUE ENGINEERING: FROM 3D PRINTING TO STEM CELL THERAPY.....	101-106
Nada HA. Al-Nuaimi, Saher S. Gasgoos. EFFECT OF CHICKEN EGG SHELL PASTE ON ENAMEL SURFACE MICROHARDNESS AND COLOUR CHANGE OF ARTIFICIAL CARIOUS LESIONS CREATED ON PERMANENTLY EXTRACTED TEETH.....	107-112
Ali Sabah Abbas, Hind Taher Jarjees. EVALUATION THE EFFECT OF THE ADDITION OF ZIRCONIUM OXIDE AND TITANIUM DIOXIDE NANOPARTICLES ON SHEAR BOND STRENGTHS OF ORTHODONTIC ADHESIVE: IN-VITRO STUDY.....	113-121

Marwa H. Abdullah, Sawsan H. Aljubori. EVALUATION OF THE EFFECT OF DIFFERENT INTRAORIFICE BARRIER MATERIALS ON CORONAL MICRO LEAKAGE OF ENDODONTIC ALLY TREATED TEETH BY USING MICRO-COMPUTED TOMOGRAPHY TECHNOLOGY (A COMPARATIVE IN VITRO STUDY).....	122-130
Makhlynets NP, Prots HB, Ozhogan ZR, Pantus AV, Yatsynovych VI. PREVENTIVE PLASTIC OF BUCCAL FRENUM IN COMPLEX TREATMENT OF PATIENTS WITH ACQUIRED MAXILLOMANDIBULARANOMALIES.....	131-135
Geetika Patel M, Nidhi, Karan Ramlal Gupta, Manish Kumar Gupta, Sudhir Kumar Gupta, Krupa S. THE IMPACT OF CLIMATE CHANGE ON INFECTIOUS DISEASES: A COMPREHENSIVE ANALYSIS OF VECTOR-BORNE DISEASES, WATER-BORNE DISEASES, AND PUBLIC HEALTH STRATEGIES.....	136-142
Volodymyr Gavrysyuk, Ievgeniia Merenkova, Yaroslav Dziublyk, Galyna Gumeniuk, Mykola Gumeniuk. REFRACTORY PULMONARY SARCOIDOSIS: INCIDENCE AFTER TREATMENT WITH METHYLPREDNISOLONE AND/OR METHOTREXATE IN PATIENTS WITH NEWLY DIAGNOSED DISEASE.....	143-147
Tsvetkova M.A., Kovalenko A.Yu. ORTHODONTIC TREATMENT ALGORITHM OF PATIENTS WITH A BURDENED DRUG ANAMNESIS. DRUGS THAT REDUCE BONE MINERAL DENSITY.....	148-152
Devanshu Patel J, Aparna vikal, Vinay Kumar HK, Aejaz Ahmadh, Krishana Kumar Sharma, Asha K. THE MICROBIOME AND METABOLIC DISORDERS: THE LINK BETWEEN THE GUT MICROBIOTA AND METABOLIC SYNDROME.....	153-158
Liubov Kobak, Orest Abrahamovych, Uliana Abrahamovych, Andriy Maksymuk, Ruslana Ivanochko. DIAGNOSTIC VALUE OF LABORATORY MARKERS OF SYNTROPIC LESIONS OF THE CIRCULATORY SYSTEM ORGANS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.....	159-164
Sriniwas Vishnu Yadkikar, Komal Patel, Renuka Jyothi R, Richard Swami, Syam Bhargavan, Sandeep Bishnoi. INNOVATIONS IN ORTHOPEDIC SURGERY: MINIMALLY INVASIVE TECHNIQUES FOR JOINT REPLACEMENT AND REPAIR.....	165-169
Kordeva S, Tchernev G, Ivanov L, Broshtilova V. "THE DANGEROUS BRASSIERE" AND THE NEVUS ASSOCIATED POLYPOID MELANOMA: CONNECTION SEEMS PLAUSIBLE?.....	170-175
Kavyn Vasyl. COMPARISON OF THE RESULTS OF STUDYING BY THE STUDENTS OF THE "CLINICAL ANATOMY AND OPERATIVE SURGERY" MODULE WITH DIFFERENT FORMS OF THE EDUCATIONAL FORMS OF THE EDUCATIONAL PROCESS IN CONDITONS OF SOCIAL SHOCKS IN UKRAINE.....	176-179
N.P. Voloshina, V.V. Vasilovsky, T.V. Negreba, V.M. Kirzhner, I.K. Voloshyn-Haponov. THE RELATIONSHIP BETWEEN THE DURATION OF REMISSIONS AFTER THE ONSET, THE SEVERITY OF THE RELAPSES AGAINST THE BACKGROUND OF DIFFERENT DURATION OF THE RELAPSING STAGE AND THE NATURE OF THE PROGNOSIS IN SECONDARY-PROGRESSIVE MULTIPLE SCLEROSIS.....	180-184
Phool Chandra, Natwar lal Vyas, Geetika Patel M, Malathi H, Radhika, Vinay Kumar HK. CARDIAC REHABILITATION: IMPROVING OUTCOMES FOR PATIENTS WITH HEART DISEASE.....	185-190
N.V. Avramenko, G.V. Bachurin, Yu.S. Kolomoets, O.A. Nikiforov. REPRESENTATION OF KIDNEY DAMAGE AT THE MOLECULAR LEVEL IN PATIENTS WITH UROLITHIASIS BASED ON THE STUDY OF ENZYMATIC TEST INDICATORS.....	191-197
Teremetskyi VI, Rusnak LM, Avramova OYe, Gorbenko AS, Kyrychenko TS. CORRELATION BETWEEN THE RIGHT TO HEALTH CARE AND THE RIGHT TO HOUSING WITHIN MEDICAL AND LAW- ENFORCEMENT PRACTICE IN TERMS OF THE COVID-19 PANDEMIC.....	198-204
Dilip Kumar Pati, Piyush Mittal, Arvind Verma, Devanshu Patel J, Asha. K, Kanika Pundir. PSORIASIS PATHOGENESIS: INSIGHTS FROM TRANSCRIPTOMICS AND PROTEOMICS STUDIES OF KERATINOCYTES....	205-211
Garashchenko O.O., Konovalenko V.F. ANALYSIS OF PLASMA MIRNA-497 LEVELS IN THE BLOOD OF PATIENTS WITH BREAST CANCER.....	212-216
Geetika Patel M, Varshini B, Anju Mandal, Deepthi Krishna, Vaibhav Rastogi, Madhumati Varma. THE ROLE OF GENETICS IN DISEASE DIAGNOSIS AND TREATMENT MITOCHONDRIAL RESPIRATORY CHAIN DYSREGULATION IN GENOMIC MEDICINE.....	217-226
Kordeva S, Broshtilova V, Batashki I, Tchernev G. BULGARIAN PATIENT WITH ATROPHODERMA OF PASINI AND PIERINI-DESCRIPTION OF A CASE AND SHORT UPDATE.....	227-231

Shypunov V.G, Strafun S.S, Borzykh A.V, Borzykh N.A, Zahovenko M.A. PECULIARITIES OF USING A NEUROVASCULARIZED FLAP ON THE SURAL ARTERY IN PLASTIC SURGERY OF GUNSHOT DEFECTS ON THE FOOT AND LOWER LEG.....	232-236
Igor Morar, Oleksandr Ivashchuk, Sergiy Ivashchuk, Volodymyr Bodiaka, Alona Antoniv. MICROBIOLOGICAL FEATURES OF A LAPAROTOMY WOUND COMPLICATED BY POSTOPERATIVE EVENTRATION AGAINST THE BACKGROUND OF AN ONCOLOGICAL PROCESS.....	237-242
Vadim V. Klimontov, Kamilla R. Mavlianova, Jilia F. Semenova, Nikolay B. Orlov. CIRCULATING PEPTIDES OF THE TNF SUPERFAMILY AND TNF RECEPTOR SUPERFAMILY IN SUBJECTS WITH TYPE 1 DIABETES: RELATIONSHIPS WITH CLINICAL AND METABOLIC PARAMETERS.....	243-248
Rurua Magda, Sanikidze Tamar, Machvariani Ketevan, Pachkoria Elene, Ormotsadze Gorge, Intskirveli Nino, Mikadze Ia, Didbaridze Tamar, Ratiani Levan. CORRELATIVE ASSOCIATION OF OXYGENATION AND SEPSIS PANELS WITH THE USE OF ACE2 INHIBITORS AND WITHOUT IT IN THE CONDITIONS OF SEPTIC SHOCK IN COVID-19-INFECTED AND NON-INFECTED PATIENTS (COHORT STUDY).....	249-253
Vladyslava Kachkovska. ASSOCIATION BETWEEN GLN27GLU POLYMORPHISM IN THE B2 ADRENERGIC RECEPTOR GENE AND OBESITY RISK IN PATIENTS WITH EARLY-ONSET AND LATE-ONSET BRONCHIAL ASTHMA.....	254-258
Lazarenko H.O, Lazarenko O.M, Shaprinskyi V.V, Semenenko N.V. INFLUENCE OF VASCULAR STENT SURFACE TREATMENT WITH AN ADAPTIVE COMPOSITION (ADC) FOR IMPROVING ITS BIOCOMPATIBILITY AND RESTENOSIS PREVENTION.....	259-263
Duve K.V. THE PREVALENCE OF C3953T IL1B GENE AND G308A TNFA GENE POLYMORPHIC VARIANTS IN THE PATIENTS WITH DIFFERENT TYPES OF ENCEPHALOPATHIES.....	264-269
Levandovskiy R, Belikova N, Belikov O, Sorokchan M, Roschuk O. EVALUATION OF THE CLINICAL CONDITION OF THE ORAL CAVITY BEFORE ADHESIVE SPLINTING OF MOVABLE TEE TH.....	270-274
Bakhtiyarov Kamil Rafaelevich, Ivantsova Margarita Vladimirovna, Kukes Ilya Vladimirovich, Ignatko Irina Vladimirovna, Glagovsky Pavel Borisovich. METABOLOMIC MARKERS OF ENDOMETRIOSIS: PROSPECTS.....	275-279
Jain SK, Komal Patel, Kavina Ganapathy, Firoz Khan, Satyaapir Sahu, Ashok Kumar Singh. LAPAROSCOPIC APPROACH TO A GIANT RUPTURED SPLENIC CYST: A CHALLENGING CASE REPORT.....	280-283
ManojRameshachandra Vyas, Phool Chandra, Rachit Jain, Devanshu Patel J, Manashree Avinash Mane, Shaily. CLINICAL AND OBJECTIVE TEST CHARACTERISTICS OF VESTIBULAR MIGRAINE: IMPLICATIONS FOR DIAGNOSIS AND MANAGEMENT.....	284-289
Vipin Kumar, Rakesh Ashokrao Bhongade, Vipin Kumar, Praveen Mathur, Komal Patel, Renuka Jyothi R. POSTCHOLECYSTECTOMY SYNDROME: UNDERSTANDING THE CAUSES AND DEVELOPING TREATMENT STRATEGIES FOR PERSISTENT BILIARY SYMPTOMS AFTER GALLBLADDER REMOVAL.....	290-296
Georgi Tchernev. LOSS OF EFFICACY OF ADALIMUMAB IN HIDRADENITIS SUPPURATIVA: FOCUS ON ALTERNATIVES.....	297-300

THE PREVALENCE OF C3953T IL1 β GENE AND G308A TNF α GENE POLYMORPHIC VARIANTS IN THE PATIENTS WITH DIFFERENT TYPES OF ENCEPHALOPATHIES

Duve K.V.

I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine Ternopil, Ukraine.

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 IL1 β C3953T gene polymorphism and TNF α 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 IL1 β gene and G308A of the TNF α 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 IL1 β gene and G308A of the TNF α gene in patients with CTE, SVD, CAIE, and PIE compared to individuals of the control group was performed. The 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 and 53.85% versus 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, respectively. In addition, in the group of patients with PIE, the distribution of genotype frequencies of the polymorphic variant C3953T of the IL1 β gene probably differed from the data of patients with CTE, SVD, and PIE ($\chi^2=28.64$; $p<0.001$), and in the group of patients with CAIE, the distribution of genotype frequencies of the polymorphic variant G308A of the TNF α gene probably differed from the data of patients with SVD and PIE ($\chi^2=24.91$; $p=0.002$). Analyzing the odds ratio and its confidence interval for the genotypes of polymorphic variants C3953T of the IL1 β gene and G308A of the TNF α gene in patients with CTE, SVD,

CAIE, and PIE, it was established that the presence of the C/T genotype of the IL1 β gene increases the risk of encephalopathy in patients with PIE by 8.0 times, and the presence of the G/A genotype of the TNF α gene increases the risk of encephalopathy in patients with PIE by 9.4 times.

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 IL1 β gene and G308A of the TNF α 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 IL1 β gene increases the risk of the occurrence and/or progression of PIE by 8.0 times, and the presence of the G/A genotype of the TNF α 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 IL1 β gene, G308A TNF α 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 $\leq 95\%$. 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 IL1 β C3953T gene polymorphism and TNF α 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 IL1 β gene and G308A of the TNF α 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 (Clever 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 (Clever 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.

Gene and polymorphism, rs	The size of the restriction/amplified fragments and the corresponding genotype
<i>IL-1β C3953T, rs1143634</i>	Genotype CC: 138 and 112 bp. Genotype CT: 250, 138 and 112 bp. Genotype TT: 250 bp.
<i>TNFα G308A, rs180062</i>	Genotype GG: 87 and 20 bp Genotype GA: 107, 87 and 20 bp Genotype AA: 107 bp.

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, χ^2), calculated using Pearson's formula: $p^2 + 2pq + q^2 = 1$ (Hardy-Weinberg equilibrium), was carried out using Pearson's χ^2 -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 IL1 β 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 C/T polymorphism of the IL1 β 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 TNF α 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 TNF α 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 IL1 β 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 C/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 IL1 β 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 IL1 β 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, IL1 β gene genotype frequency distribution probably differed from the data of patients with CTE, SVD, and PIE ($\chi^2 = 28.64$; $p < 0.001$).

The results of the frequency distribution of TNF α 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 TNF α gene was not detected. Comparing the distribution of genotypes of the TNF α 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 TNF α 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 TNF α gene genotypes probably differed from the data of patients with SVD and PIE ($\chi^2 = 24.91$; $p = 0.002$).

Analyzing the odds ratio and its confidence interval for the genotypes of the IL1 β 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 IL1 β 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 TNF α 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 (IL1 β) 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. IL1 β is also considered an important mediator of inflammation after cerebrovascular ischemia [14]. There is evidence that IL1 β , 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 IL1 β 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 IL1 β gene in patients with

Table 2. *IL1 β gene polymorphism according to the Hardy-Weinberg law in patients with different types of encephalopathies.*

Genotype		CTE		SVD		CAIE		PIE		Control	
		expected	Available	expected	available	expected	Available	expected	Available	expected	Available
IL1β gene polymorphism											
Homozygotes that occur frequently	C/C	16,96	16	14,22	14	22,15	22	8,66	7	10,08	10
Heterozygotes	C/T	8,08	10	3,56	4	3,69	4	12,69	16	1,83	2
Homozygotes, which are rare	T/T	0,96	0	0,22	0	0,15	0	4,65	3	0,08	0
χ^2 , p		$\chi^2=1,47$; p>0,05		$\chi^2=0,28$; p>0,05		$\chi^2=0,18$; p>0,05		$\chi^2=1,77$; p>0,05		$\chi^2=0,10$; p>0,05	

Note. * – statistically significant result.

Table 3. *Polymorphism of the TNF α gene according to the Hardy-Weinberg law in patients with various types of encephalopathies.*

Genotype		CTE		SVD		CAIE		PIE		Control	
		expected	available	expected	available	expected	available	expected	available	expected	available
TNFα gene polymorphism											
Homozygotes that occur frequently	G/G	18,62	18	8	9	22,15	22	15,38	14	11,02	11
Heterozygotes	G/A	6,77	8	8	6	3,69	4	9,23	12	0,96	1
Homozygotes, which are rare	A/A	0,62	0	2	3	0,15	0	1,38	0	0,02	0
χ^2 , p		$\chi^2=0,86$; p>0,05		$\chi^2=1,13$; p>0,05		$\chi^2=0,18$; p>0,05		$\chi^2=2,34$; p>0,05		$\chi^2=0,02$; p>0,05	

Note. * – statistically significant result.

Table 4. *IL1 β and TNF α gene polymorphisms in patients with different types of encephalopathies.*

Genotype	CTE		SVD		CAIE		PIE		Control	
	n	%	n	%	n	%	n	%	n	%
IL1β gene polymorphism										
C/C	16	61,54	14	77,78	22	84,62	7	26,92	10	83,33
C/T	10	38,46	4	22,22	4	15,38	16	61,54	2	16,67
T/T	0	0	0	0	0	0	3	11,54	0	0
χ^2 (EP/CG), p	$\chi^2=1,80$; p=0,179		$\chi^2=0,14$; p=0,709		$\chi^2=0,01$; p=0,920		$\chi^2=10,71$; p=0,005*		–	
χ^2 , p	$\chi^2=28,64$; p<0,001*; p _{1-4, 2-4, 3-4} <0,05*									
TNFα gene polymorphism										
G/G	18	69,23	9	50,00	22	84,62	14	53,85	11	91,67
G/A	8	30,77	6	33,33	4	15,38	12	46,15	1	8,33
A/A	0	0	3	16,67	0	0	0	0	0	0
χ^2 (EP/CG), p	$\chi^2=2,29$; p=0,131		$\chi^2=5,80$; p=0,055		$\chi^2=0,36$; p=0,550		$\chi^2=5,22$; p=0,022*		–	
χ^2 , p	$\chi^2=24,91$; p=0,002*; p _{2,3, 3-4} <0,05*									

Note. * – statistically significant result.

Table 5. *Odds ratios for IL1 β genotypes in patients with different types of encephalopathies.*

Type of encephalopathy	IL1β gene polymorphism					
	C/C		C/T		T/T	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
CTE	0,32	0,06–1,77	3,13	0,56–17,30	0,47	0,01–25,18
SVD	0,70	0,11–4,59	1,43	0,22–9,38	0,68	0,01–36,35
CAIE	1,10	0,17–7,03	0,91	0,14–5,81	0,47	0,01–25,18
PIE	0,07*	0,01–0,42	8,00*	1,44–44,30	3,72	0,18–77,97

Note. * – statistically significant result.

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

Type of encephalopathy	<i>TNFα</i> gene polymorphism					
	GG		GA		AA	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
CTE	0,20	0,02–1,86	4,89	0,54–44,57	0,47	0,01–25,18
SVD	0,09*	0,01–0,86	5,50	0,57–53,22	5,65	0,27–119,85
CAIE	0,50	0,05–5,03	2,00	0,20–20,10	0,47	0,01–25,18
PIE	0,11*	0,01–0,95	9,43*	1,06–84,04	0,47	0,01–25,18

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-1 β is highest in TT genotype and lowest in CC [17]. Licastro F. et al. investigated whether IL-1 β 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-1 β (IL-1 β) genes. The IL-1 β +3953 polymorphism influenced survival in AD patients and those with the TT genotype and without the APOE ϵ 4 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-1 β , IL-6, IL8, and TNF α activate cells of innate immunity. In addition, TNF α increases the cytotoxic properties of NK cells and the production of IFN γ , 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 TNF α G308A polymorphism – a single nucleotide polymorphism involving guanine to adenine substitution at position 308 in the promoter region of the TNF α 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 TNF α 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].

Conclusion.

1. Analyzing the frequency distribution of genotypes of the C3953T polymorphic variant of the IL1 β 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 ($\chi^2=28.64$; $p<0.001$).

2. Analyzing the frequency distribution of genotypes of the polymorphic variant G308A of the TNF α 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 ($\chi^2=24.91$; $p=0.002$).

3. Analyzing the odds ratio and its confidence interval for the genotypes of polymorphic variants C3953T of the IL1 β gene and G308A of the TNF α gene in patients with CTE, SVD, CAIE, and PIE, it was established that the presence of the C/T genotype of the IL1 β 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 TNF α 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 IL1 β and TNF α genes in the genetic panel of patients with PIE to prescribe adequate therapy to prevent disease progression.

REFERENCES

1. Ding C, Wu Y, Chen X, et al. Global, regional, and national burden and attributable risk factors of neurological disorders:

- The Global Burden of Disease study 1990-2019. *Front Public Health*. 2022;10:952161.
2. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:459-480.
 3. Erkinen MG, Berkowitz AL. A Clinical Approach to Diagnosing Encephalopathy. *Am J Med*. 2019;132:1142-1147.
 4. Frontera JA, Melmed K, Fang T, et al. Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care*. 2021;1-14.
 5. Usychenko K.M. "Vzaimozv'язok alelnoho polimorfizmu heniv tsytokiniv ta stupeni fibrozu u khvorykh na khronichni hepaty virusnoi etiologii." 2023.
 6. Kashchenko O.A, O.V. Denysenko, O.V. Onufriienko, et al. Rol neuroimunnykh mekhanizmiv i zapalennia v patohenezi epilepsii. *Dosiahnennia biolohii i medytsyny*. 2016:2.
 7. Manzhaliy E.H. Zalezhnist tiazhkosti depresii u khvorykh z pechinkovoiu entsefalopatiieiu vid rivnia tsytokiniv. *Likarska Sprava*. 2016;5-6:56-65.
 8. Yablon O.S, T.V. Bondarenko. Prozapalni tsytokiny (IL-6, FNP-A) yak prohnostychnyi chynnyk vazhkosti urazhennia mozku u donoshenykh novonarodzhenykh. *Neonatolohiia, khirurhiia ta perynatalna medytsyna 2019:IX,2:16-21*.
 9. Peck MM, Maram R, Mohamed A, et al. The Influence of Pro-inflammatory Cytokines and Genetic Variants in the Development of Fibromyalgia: A Traditional Review. *Cureus*. 2020;12:e10276.
 10. Li X, Zhu J, Peng Y, et al. Association of Polymorphisms in Inflammatory Cytokines Encoding Genes With Anti-N-methyl-D-Aspartate Receptor Encephalitis in the Southern Han Chinese. *Front Neurol*. 2020;11:553355.
 11. Hollegaard MV, Bidwell JL. Cytokine gene polymorphism in human disease: on-line databases, supplement 3. *Genes Immun*. 2006;7:269-276.
 12. Onishchenko N.V, Riabokon O.V Zalezhnist perebihu vitrianoi vispy u doroslykh vid henetychnoho polimorfizmu henu interleikinu-10 (RS 1800872). *Zbirnyk tez dopovidei naukovo-praktychnoi konferentsii z mizhnarodnoiu uchastiu molodykh vchenykh ta studentiv «Aktualni pytannia suchasnoi medytsyny i farmatsii 2019» (Zaporizkyi derzhavnyi medychnyi universytet, m. Zaporizhzhia, 13-17 travnia 2019 r.)*. – Zaporizhzhia: ZDMU. 2019:87-88.
 13. O.A. Oshlianska, A.H. Artsymovych, Z.I. Rossokha, et al. Kryvova mozhyvosti vykorystannia alelnoho polimorfizmu heniv interleikinu-6 g-174c ta faktora nekrozu pukhlyny- α g308a dlia prohnovuvannia perebihu yuvenilnoho idiopatychnoho artrytu. *Ukrainskyi revmatolohichnyi zhurnal*. 2021;2:1-9.
 14. Hassan SA, Arbab MA, Abdelrahman SF, et al. The Significance of Mutation in IL-1 β Gene and Circulatory Level for Prediction of Trauma Severity and Outcome in Traumatic Cerebral Hemorrhagic Contusion. *J Acute Med*. 2020;10:70-76.
 15. Misra S, Kumar P, Kumar A, et al. Genetic association between inflammatory genes (IL-1 α , CD14, LGALS2, PSMA6) and risk of ischemic stroke: A meta-analysis. *Meta Gene*. 2016;8:21-29.
 16. Murray KN, Parry-Jones AR, Allan SM. Interleukin-1 and acute brain injury. *Front Cell Neurosci*. 2015;9:18.
 17. Aguet F, Barbeira A, Bonazzola R, et al. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science*. 2020;369:1318-1330.
 18. Licastro F, Veglia F, Chiappelli M, et al. A polymorphism of the interleukin-1 beta gene at position +3953 influences progression and neuro-pathological hallmarks of Alzheimer's disease. *Neurobiol Aging*. 2004;25:1017-22.
 19. Duan R, Wang N, Shang Y, et al. TNF- α (G-308A) Polymorphism, Circulating Levels of TNF- α and IGF-1: Risk Factors for Ischemic Stroke-An Updated Meta-Analysis. *Front Aging Neurosci*. 2022;14:831910.
 20. Satterfield BC, Wisor JP, Field SA, et al. TNF α G308A polymorphism is associated with resilience to sleep deprivation-induced psychomotor vigilance performance impairment in healthy young adults. *Brain Behav Immun*. 2015;47:66-74.
 21. Wang T. TNF-alpha G308A polymorphism and the susceptibility to Alzheimer's disease: an updated meta-analysis. *Arch Med Res*. 2015;46:24-30.e1
 22. DiSabato D. J, N. Quan, J. P. Godbout. Neuroinflammation: the devil is in the details. *J Neurochem*. 2016;139:136-153.
 23. Shulyatnikova T, Verkhatsky A. Astroglia in sepsis associated encephalopathy. *Neurochem Res*. 2020;45:83-99.