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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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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 ВИНИТИ 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 ВИНИТИ 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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ 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 შეღებვის 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 ფჩხილებში 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.

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FEATURES OF VASOMOTOR RHINITIS (VMR) IN PATIENTS WITH A HISTORY OF COVID-19 INFECTION

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Abstract.

Objective: To determine some aspects of the pathogenesis of VMR in patients with a history of COVID-19 infection and to evaluate the therapeutic efficacy of a local antihistamine drug.

Design: Data was collected from patients diagnosed with Vasomotor rhinitis (VMR) (who had COVID-19 more than 6 months ago, group I) and those without COVID-19 (group II). These patients were filtered to seasonal allergens, a history of bronchial asthma and/or bronchial hypersensitivity, chronic rhinosinusitis, nasal polyposis or sensitivity to aspirin, pregnancy, acute phase of COVID-19 infection, and use of anti-inflammatory drugs within the last 6 weeks.

Setting: First University Clinics of Tbilisi State Medical University and the National Centre of Otorhinolaryngology (Tbilisi, Georgia).

Participants: Patients diagnosed with VMR for 6 weeks or more were selected.

Methods: All patients underwent the instrumental (anterior and posterior rhinoscopy, endoscopy, rhinomanometry) examination, the cytological (eosinophils, neutrophils, and leukocytes count), and biochemical investigations of nasal smear (the content of nitric oxide (NO)) and blood serum total antioxidant activity. Patients were treated with intranasal antihistamine spray - 2 sprays 2 times a day for 10 days. All studies were performed on patients before and after treatment.

Results: No statistically reliable difference in the initial insights of the objective and subjective indicators for groups I and II were detected; the cytological examination of nasal smears showed that in patients from group I eosinophils, lymphocytes, an increased number of neutrophils and low-level of NO were revealed compared to corresponding indicators in patients from group II. The level of TAA in the blood serum of patients with VMR was lower than in healthy volunteers (especially in patients of group I).

Conclusions: In patients with VMR previously exposed to COVID-19 infection, the intensity of the oxidative stress and depletion of nasal NO were especially high, causing the abolishment of protective ability, chronic eosinophilic inflammation, and airway hyperresponsiveness. Antihistamine spray is effective for VMR treatment in groups I and II; in patients with VMR who previously had a COVID-19 infection, it is necessary to increase the treatment course duration.

Key words. Vasomotor rhinitis, COVID-19 infection, oxidative stress, Nitric oxide, eosinophilia.

Introduction.

Coronavirus disease 2019 is a systemic condition with a wide range of symptoms related to airways (e.g., cough, dyspnea, and sputum production) and other systems (diarrhea, abnormal heart rhythm, and headache) [1]. As of August 8, 2022, more than 581 million positive cases have been reported in the world, whereas the number of related deaths is over 6.4 million [2]. In Georgia, approximately 1,7 million people have been diagnosed with COVID-19, and 16,869 have died from the disorder. Meanwhile, approximately 12 billion vaccine doses have been administered worldwide. long-lasting symptoms suffered by 12.8-27.8% of patients recovering from SARS-CoV-2. It was shown that the prevalence of post-COVID-19 conditions 28 days to 12 months after COVID-19 infection was 54% in hospitalized individuals and 34% in non-hospitalized individuals [3]. A growing body of literature has shown that symptoms persist for at least several months in a substantial proportion of people affected by SARSCoV-2 [3,4]. Shortness of breath, fatigue, joint pain [5], insomnia and ageusia [5], vasomotor rhinitis, and injuries in the olfactory neuroepithelium [6] are the most commonly reported symptoms; they are, therefore, associated with the post-COVID syndrome (PCS). Given the high prevalence of the history of COVID-19 in the general population, it is crucial to understand better the long-term effects of this disease on health.

As practice has shown, rhinitis is common after the transfer of SARS-CoV-2 [7], although studies in this direction cannot be found in the literature. Rhinitis is defined as inflammation of the nasal mucosa, which occurs annually in more than 200 million individuals worldwide [8-10], placing a heavy burden on society and requiring huge costs for medical treatment.

As practice has shown, rhinitis is common after the transfer of SARS-CoV-2 [7]. Rhinitis is defined as inflammation of the nasal mucosa, which occurs annually in more than 200 million individuals worldwide [8,9], placing a heavy burden on society and requiring huge costs for medical treatment. Non-allergic perennial rhinitis, i.e. VMR is a chronic form of non-infectious rhinitis, clinical signs can last more than 9 months a year and are characterized by signs and symptoms identical to those of allergic rhinitis (rhinorrhea, nasal congestion, sneezing, and post-nasal discharge) [8-10]. Unlike allergic rhinitis, the etiology of "Nonallergic rhinopathy" (Vasomotor Rhinitis (VMR)) is unknown and is not related to IgE-mediated mechanisms, infections, structural lesions, systemic diseases, drug use, or eosinophilia. VMR was defined as "a chronic nasal condition

with symptoms that may be perennial, persistent, intermittent or seasonal and/or elicited by recognized triggers" [11]. The manifestation of symptoms of VMR can be challenged by a variety of non-specific causes, such as changes in temperature and/or humidity, strong odors, respiratory irritants, spicy foods, and alcoholic beverages. In addition, the symptoms of VMR are characterized by the release of pro-inflammatory mediators (cytokines, leukotrienes) and cell adhesion molecules (ICAM-1), which play an important role in the processes of maturation, migration, and activation of inflammatory cells (eosinophils and mast cells). There is a correlation between inflammation, the degree of hyperactivity of the nasal cavity, and the severity of symptoms of VMR. Literature data indicate the impossibility of identifying patients with VMR by classical inflammatory markers [10] there are no special diagnostic tests for vasomotor rhinitis. The diagnosis is usually based on excluding a causal relationship with allergic irritants [12].

Despite many strategies for the treatment of VMR, to this day there is no single treatment regimen; mainly intranasal corticosteroids and antihistamines are used. The first one is effective in various forms of eosinophilia and, as a rule, is ineffective in treating symptoms [13].

Our study aimed to determine some aspects of the pathogenesis of VMR in patients with a history of COVID-19 infection and to evaluate the therapeutic efficacy of a local antihistamine drug.

Materials and Methods.

The study was conducted at the First University Clinic of Tbilisi State Medical University and the National Center of Otorhinolaryngology in Tbilisi, Georgia, from 2020 to 2021.

The study's criteria for inclusion of patients are shortness of breath through the nose, runny nose, and itching in the nasal cavity for 6 weeks or more.

Exclusion criteria from the study: patients sensitized to seasonal allergens, with a history of bronchial asthma and/or bronchial hypersensitivity, chronic rhinosinusitis, nasal polyposis or sensitivity to aspirin, pregnant women, patients in the acute phase of COVID-19 infection, nicotine users, excessive alcohol users and patients who took anti-inflammatory drugs (nasal steroids or antihistamines within the last 6 weeks).

Inclusion and exclusion of patients in the study were performed according to anamnesis data.

For the correct diagnosis and differentiation among types of rhinitis, a thorough analysis of comprehensive history (anamnesis) is usually used (symptoms (i.e., duration, exposures, magnitude of reaction, patterns, and chronicity) triggers, seasonal variation, environmental influences; allergies, medical history (i.e., trauma, family, and treatment histories).

The patients with allergic rhinitis were excluded based on the allergen-specific IgE test, percutaneous skin test [13,14], and trigger identification [14]. Vasomotor rhinitis is diagnosed through exclusion; patients should have normal serum IgE levels, negative skin testing or RAST, and no inflammation on nasal cytology. The other types of rhinitis were excluded according to anamnesis data (acute viral rhinitis and rhinosinusitis, hormonal (caused by pregnancy, oral contraceptive use, and hypothyroidism), drug-induced rhinitis (angiotensin-converting enzyme inhibitors, reserpine, guanethidine, phentolamine, topical nasal decongestants, aspirin, nonsteroidal anti-inflammatory drugs, etc.), rhinitis medicaments (Repetitive use of topical alpha-adrenergic decongestant sprays) [14]. The term vasomotor implies an increased blood supply to the nasal mucosa, although this suggestion has not been proven. Symptoms mainly consist of congestion; hypersecretion; and, less commonly, pruritus and sneezing.

The diagnosis of non-allergic VMR was made based on subjective (frequency of sneezing, degree of difficulty in nasal breathing, nature, consistency, color of nasal discharge, as well as the color of swelling of the nasal mucosa, and turbinate, impaired olfactory function, general condition of the patient) and objective (anterior and posterior rhinoscopy, endoscopy (exclude patients with signs of purulent rhinitis or polyposis from the study); rhinomanometry (to assess difficulty in breathing and to exclude patients with concomitant diseases (curvature, polyposis, nasal valve insufficiency, the degree of nasal congestion)) studies [14].

The study design was approved by the Ethics Committee of the National Center of Otorhinolaryngology. After informed consent, patients were asked to complete the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire (a simple five-question, validated survey that uses a 20-point scale to capture breathing symptoms, with higher scores indicating more severe symptoms than lower scores to assess the severity of nasal obstruction) [15].

All patients were antigen-tested or had a negative PCR test for COVID-19.

The study involved 140 volunteer market vendors (Tbilisi, Georgia) aged 28 to 58 years, of which 60 (42.9%) were women, and 80 (57.1%) were men. Patients were divided into 3 groups: Group I - patients with VMR presenting more than 6 months after infection with SARS-CoV-2 (post-COVID-19 complication) (n=58 (30 women, 28 men), 41.5%); Group II - patients with VMR without COVID-19 (n=52 (32 women, 20 men), 37.1%); in the group III were included healthy volunteers (n=30 (18 women, 12 men), 21,4%) who more than 6 months didn't contract COVID-19. The Group who had contracted COVID-19 had expressed symptoms of the infection such as high temperature, cough, runny nose, and sore throat (mild severity of COVID-19); patients in this group were not hospitalized.

In all groups 28-35-year-old patients had no comorbidity and specific medication prescriptions. As for 35-40-year-old patients' hyperthyroidism, autoimmune hypothyroidism and prediabetes were marked. In the same age range third group patients had no demonstrated comorbidities. In the 40-58 -year-old patients of all groups (I, II, III) diabetes mellitus, high blood pressure, autoimmune hypothyroidism, arthritis, and arthrosis were presented (Table 1).

Persons of groups I and II underwent the instrumental examination, the cytological (eosinophils, neutrophils, and leukocytes count) and biochemical investigations of nasal smear (the content of nitric oxide (NO)) and blood serum total antioxidant activity. All studies were performed on patients before and after treatment; on 3-d and 5-th days after the beginning of treatment, the patient was scheduled to consult an

Table 1. *Demographical characteristics of the studied patients (age, gender) and comorbidities.*

	Gender		**Comorbidities**		
	male	**female**	**28-35 years**	**35-40 years**	**40-58 years-**
Group I - patients with VMR presenting more than 6 months after infection with SARS-CoV-2 (post-COVID-19 complication) (n=58)	28	30	No	Hyperthyroidism – 5 patients (2 men, 3 women); Autoimmune hypothyroidism - 3 patients (1 man, 2 women); Prediabetes - 0	Diabetes mellitus - 6 patients (4 men, 2 women); High blood pressure - 2patients (2 women); Autoimmune hypothyroidism - 1 patient (1 woman); Arthritis - 1woman Arthrosis-0
Group II - patients with VMR without COVID-19 (n=52)	20	32	No	Hyperthyroidism 3 patients (1 man, 2 women); Autoimmune hypothyroidism - 5 patients (2 men, and 3 women), Prediabetes - 2 patients (2 men)	Diabetes mellitus – 3 patients (1 man, 2 women); High blood pressure- 4 patients (3 women, 1 man); Autoimmune hypothyroidism - 2 women; Arthritis – 0; Arthrosis – 0
Group III - healthy volunteers (n=30)	12	18	No	No	Diabetes mellitus - 5 patients (2 women, 3 men); High blood pressure - 0; Autoimmune hypothyroidism – 2 patients (2 women); Arthritis – 0; arthrosis – 0.

otolaryngologist to assess the general condition and/or identify possible side effects.

Patients of groups I and II were treated for VMR with intranasal antihistamine spray- 2 sprays 2 times a day for 10 days. The healthy volunteers of group III were treated with physiological solute 2 sprays 2 times a day for 10 days. The drug's mechanism of action is based on olopatadine's ability to cause inhibition of the release of biologically active substances - inflammatory mediators (bradykinin, serotonin, histamine, leukotrienes).

The effectiveness of treatment was assessed according to the subjective complaints of patients and according to objective indicators of instrumental examination. For the assessment of the effectiveness of treatment, we used a simple 3-point system introduced and successfully tested by local clinical practice in the National Centre of Otorhinolaryngology (0 score - asymptomatic patient, 1 score - minor complaints, 2 scores - moderate complaints, 3 scores - strong, pronounced complaints (sneezing was assessed by intensity and duration)).

Nasal smears cytological examination.

All participants collected nasal smears by scraping the mucous membrane of the medial surface of both inferior turbinates with a sterile cotton swab soaked in saline. The secretions were then spread thinly onto two glass slides (one for each side) and air-dried. The slides were numbered and sent to the pathologist for examination. The smears were stained with the May-Grünwald-Giemsa stain and the eosinophil, neutrophil, and leucocyte count was recorded in terms of the number of eosinophils per high power field (HPF).

As the cells were unevenly distributed in smears, the eosinophils, neutrophils, and leucocytes were counted in at least 50 HPFs, and the average count was recorded. This was done for smears from both the left and right nostrils; finally, an average of the two counts was calculated.

To prevent subjective judgment by the investigator examining the smears, all the smears from patients and controls were coded before they were sent to the pathologist. The same observer examined all the smears.

Measurement of nitric oxide metabolites (nitrite and nitrate) level (total NOx) in nasal smears.

The samples were collected from all patients from the mucous membrane of the medial surface of both inferior turbinates with insertion for 30 seconds of absorbent paper strips, which were placed in separate tubes. Before measurement of the metabolites (nitrite and nitrate) level, the paper strips were placed into physiological saline for 3 minutes.

The level of NOx in the saline samples was determined by a modified method by Miranda et al. using Griess Reagent. The absorbance was measured at 540 nm with a microplate reader (Multiscan GO, Thermo Fischer Scientific, Finland). The standard curve for $NaNO_2$ was used to calculate the metabolites (nitrite and nitrate) (total NOx) concentration in the samples [16].

Measurement of total antioxidant activity (TAA) of blood serum.

TAA was determined in deproteinized blood serum by using the 2.2-diphenyl-1-picryl-hydrazine (DPPH)-scavenging assay [17]. Serum samples (1 ml) were deproteinized by adding 3 ml of acetonitrile and centrifuging them for 10 min (4°C, 9500g). A supernatant was immediately collected, and 1 ml was transferred to a tube, subsequently, 3 ml of DPPH was added, and the resultant solution's absorbance was read at 515 nm. A calibration curve was built with the use of Gallic acid, wherein the absorbance values were interpolated, and the results were expressed as equivalents of Gallic acid (%).

Statistical analysis.

To compare the rank alterations, reflected in scores, of the subjective and objective characteristics of patients in groups I and II before and after treatment, the nonparametric Mann-Whitney U test was used. A P value of less than 0.05 indicated a statistically significant difference.

Statistical significance of differences between nasal smear cytologic markers (eosinophil, neutrophil, lymphocyte counts, NO content), and blood plasma TAA levels was assessed using ANOVA ($p< 0.05$).

Results.

Results of patients' subjective and objective (instrumental) examination:

In Tables 2 and 3, subjective and objective indicators of patients with VMR in groups I and II are presented before, on the 3rd and 5th days after the initiation of treatment, as well as at the end of the treatment. The study results indicate no statistically reliable difference in the insights of the objective and subjective indicators for groups I and II before the treatment (Table 2, 3, 4). At the same time, the positive results of treatment appear faster in patients of group II with VMR who have not undergone COVID-19; these patients showed an improvement in subjective and objective indicators already on the 5th day of treatment. On the 5th day of the treatment, subjective indicators of disease state sharply decreased (Table 2) and the dynamics of objective indicators were positive in 64% of patients with VMR from group II (Table 3); on the 10th day of treatment, positive dynamics were revealed in 78% of patients of group II.

In group I patients with VMR who underwent COVID-19 more than 6 months ago, on the 5th day of treatment the positive dynamic was detected in 52% of patients, and on the 10th day - in 62% of patients. An important improvement in the I group patients' state was recorded only by the end of treatment. These data allow us to conclude that in patients with VMR on the phone of previous COVID-19 infection, it is necessary to increase the duration of the course of treatment.

Results of nasal smears cytological examination.

In Figure 1 results of the cytological examination of nasal smears of healthy volunteers, and patients of groups I and II with VMR before the beginning and after the treatment.

The average number of eosinophils in nasal smears of healthy volunteers was 0±0,2, neutrophils - 1.5±0.5 and lymphocytes -

Table 2. *Average number of subjective indicators in patients with VMR of groups I and II (0 score - asymptomatic patient, 1 score - minor complaints, 2 scores - moderate complaints, 3 scores - strong, pronounced complaints (sneezing was assessed by intensity and duration)).*

	Before the beginning of treatment		**3 days after the beginning of the treatment**		**5 days after the beginning of the treatment**		**at the end of the treatment**	
Groups	I group	II group	I group	II group	I group	II group	I group	II group
Sneezing	2,9±0,4	2.6±0,3	2,7±0,3	2,6±0,3	2,1±0,4	1,1±0,2* **	0,8±0,3*	0,2±0,1* **
Discharge from the nose	2,5±0,3	2,2±0,4	2,2±0,4	2,2±0,3	2,0±0,4	0,5±0,3* **	1,9±0,4	0,1±0,1* **
Obstruction of nasal breathing (nasal congestion)	2,9±0,4	2,5±0,4	2,4±0,4	2,3±0,4	2,4±0,5	0,6±0,1* **	1,0±0,3*	0,3±0,1* **
Total score	8,3±0,4	7,3±0,4	7,3±0,4	7,1±0,3	6,5±0,4*	2,2±0,2* **	3,7±0,4*	0,6±0,1* **

**P<0.05 – the difference between the studied parameters and the initial state.*
***p<0.05 – the difference in studied parameters between the groups.*

Table 3. *Objective indicators of patients with VMR in groups I and II.*

	Before the beginning of treatment		**3 days after the beginning of the treatment**		**5 days after the beginning of the treatment**		**at the end of the treatment**	
Groups	I group	II group	I group	II group	I group	II group	I group	II group
Endoscopy	2,9±0,3	2,8±0,3	2,6±0,3	2,1±0,2*	2,4±0,5	0,3±0,1* **	2,0±0,5*	0,2±0,1* **
Rhinomanometry	2,3±0,2	2,2±0,2	2,8±0,3	2,8±0,4	2,1±0,6	0,6±0,2* **	1,6±0,4*	0,3±0,1* **
Narrowing of the nasal passage	2,8±0,3	2,7±0,3	2,8±0,3	2,4±0,3	2,0±0,5	0,7±0,2* **	1,1±0,4*	0,4±0,2* **
Total score	8,0±0,3	7,7±0,3	8,2±0,3	7,3±0,3*	6,5±0,5*	1,6±0,2* **	4,7±0,4*	0,9±0,1* **

**P<0.05 – the difference between the studied parameters and the initial state.*
***p<0.05 – the difference in studied parameters between the groups.*

Table 4. *Statistical significance of the differences between the parameters of subjective and objective characteristics of I and II groups of patients before the beginning and after the end of treatment (Wilcoxon matched-pairs signed-rank test).*

N	**Characteristics**	**Before the beginning of treatment**		**At the end of the treatment**	
		Z	**p-value**	**Z**	**p-value**
1	Sneezing	1.388	0.1650	4.106	<0.001
2	Discharge from the nose	0.431	0.666	4.372	<0.001
3	Obstruction of Nasal Breathing (nasal congestion)	1.388	0.165	3.912	<0.001
4	Endoscopy	1.277	0.201	4.372	<0.001
5	Rhinomanometry	0.188	0.850	4.372	<0.001
6	Narrowing of the nasal passage	1.136	0.255	4.197	<0.001

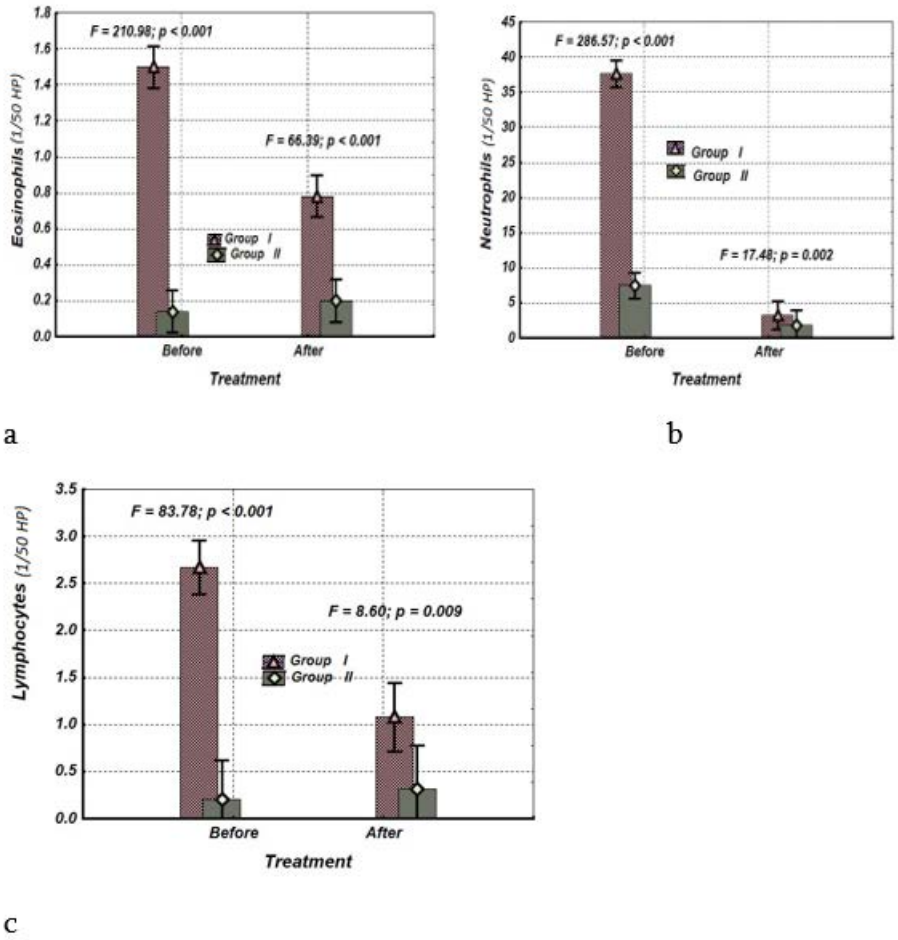

Figure 1. *An average number of the eosinophils (a), neutrophils (b), and leucocytes (c) in the nasal smears (1/50 HP) of patients of groups I and II with VMR before and after the treatment.*

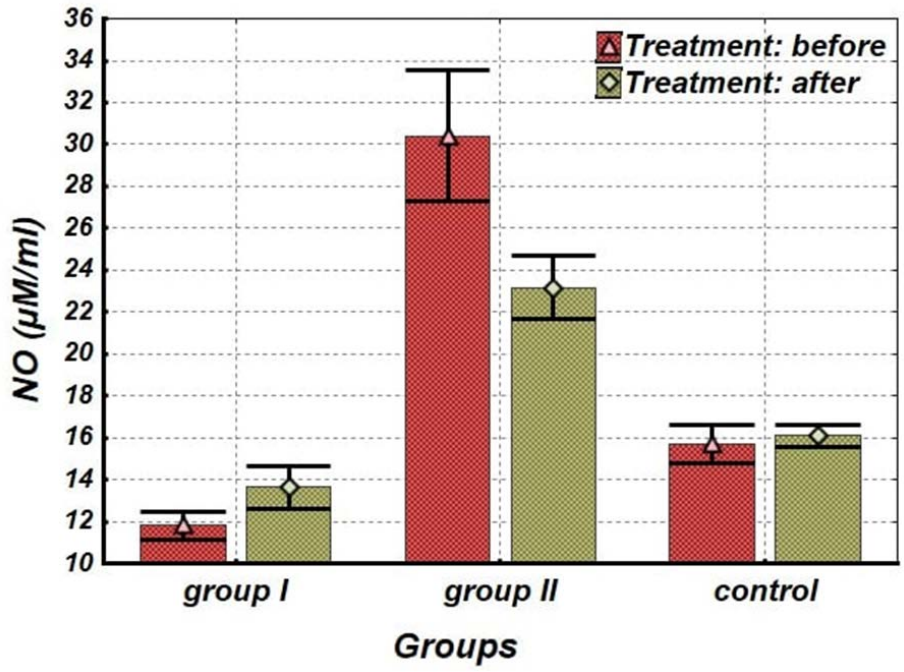

Figure 2. *Total NOx level in the nasal smears of healthy volunteers, and patients of groups I and II with VMR before the beginning (1) and after the treatment (2).*

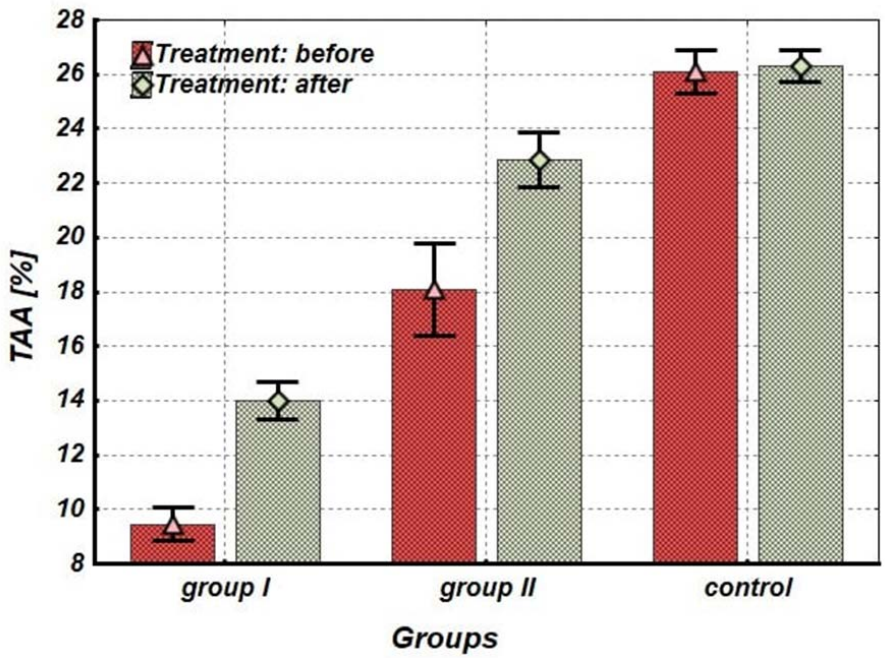

Figure 3. *TAA level of blood serum of healthy volunteers, and patients of groups I and II with VMR before the beginning (1) and after the treatment (2) (calibration curve was built with the use of Gallic acid, wherein the absorbance values were interpolated, and the results were expressed as equivalents of Gallic acid (%)).*

0±0,3; these data matched the normative values of inflammatory cells in the nasal smears of adults detected by Zhang Y. et al (2014) [18]. In nasal smears of patients with VMR of the group I mean eosinophils, lymphocytes, and neutrophils counts before the treatment were importantly higher than the respective insights in patients of the control group; in the II group mean eosinophil and lymphocytes counts were not different and neutrophils number was 4.4 times more than the respective insights in healthy volunteers.

After treatment, the values of the studied indicators decreased significantly, however, in the patients of the first group, they still significantly exceeded the control level, while in the patients of the second group, they approached the control.

Results of the Measurement of Total NOx Level.

Figure 2 shows the results of the measurement of total NOx level in the nasal smears of healthy volunteers, and patients of groups I and II with VMR before the beginning and after the treatment.

As seen in Figure 2, the level of NO in nasal smears of patients with VMR developed after more than 6 months of COVID-19 infection (group I) was 69%, and in patients with VMR who did not undergo COVID-19 (group II) - 189% of the level in healthy volunteers.

After the treatment, the level of NO in both studied groups was changed towards the control insights (group 1: F = 1.35; p = 0.258; group 2: F = 12.01; p = 0.001).

Results of measurement of total antioxidant activity (TAA) of blood serum.

Figure 3 shows the results of the measurement of TAA of blood serum of healthy volunteers, and patients of groups I and II with VMR before the beginning and after the treatment.

As seen in Figure 3, the level of TAA in the blood serum of patients with VMR (groups I, and II) was lower than the level of TAA in the blood serum of healthy volunteers (by 66% and 31%, respectively). After the treatment level of TAA in both studied groups was increased (group 1: F = 2.43; p = 0.135; group 2: F = 1.15; p = 0.297), but in patients with VMR developed after more than 6 months of COVID-19 infection (group I), its level was statistically significantly lower than in control (F = 8,6; p = 0.001).

Discussion.

It has been reported that about 80% of hospitalized patients with COVID-19 for several months after discharge had long-term health complications, manifested by at least one symptom, particularly fatigue and dyspnea, disorders in the respiratory tract [3-6]. Despite numerous studies of patients with post-COVID complications, this clinical condition is not yet well understood and its biomarkers and their close association with various residual symptoms after recovery have not been established. The pathophysiology, risk factors, and management of post-COVID-19 are currently poorly understood.

We studied indicators of inflammation and oxidative stress in the patients with VMR, who had COVID-19 more than 6 months ago (group I) and did not have COVID-19 (group II). Our study results show that no statistically significant differences have been found between subjective characteristics and the values of objective indicators of instrumental examination in patients of groups I and II.

Results of cytological examination show, that in the nasal smears of patients with VMR who had COVID-19 more than 6 months before (group I), eosinophils, lymphocytes, and neutrophils counts were importantly higher, and the level

of NO in nasal smears of these patients was 64% lower than the respective insights in healthy volunteers. In nasal smears of patients without COVID-19 infection (group II) neutrophil number was 4.4 times higher, the level of NO was 31% lower, and mean eosinophil and lymphocyte counts were not different from the respective insights in healthy volunteers.

Vasomotor rhinitis is a term often used to describe rhinitis symptoms associated with nonallergic, non-infectious triggers with no clear etiology after the conclusion of an exhaustive search for a diagnosis. The pathophysiology of nonallergic rhinitis is complex, with still much to be discovered. The disease is characterized by heterogeneity in the clinical phenotypes and inflammatory profile [19]. VMR diagnosis is often made by exclusion according to any features of allergy in the nasal cytology (eosinophils) and the nasal allergen provocation test [20,21]. Hence, more studies and reliable biomarkers are needed to identify the VMR endotype accurately.

As follows from the results of the cytological examination of nasal smears of patients with VMR who had COVID-19 more than 6 months before, eosinophils, lymphocytes, and an increased number of neutrophils were revealed compared to corresponding indicators in patients with VMR without COVID-19. These data suggest that the pathogenesis of the VMR developed after COVID-19 infection likely includes the nonspecific release of histamine and chronic eosinophilic inflammation [22].

Sustained inflammation contributes to the systemic hyperinflammatory state and hyper-coagulopathy which are cardinal pathological mechanisms of severe stages of viral infection and in the development and progression of further complications by disrupting tissue (via autoantibodies), blood flow (e.g. immune thrombosis) and neurotransmitter metabolism (e.g. excitotoxicity) [23].

Investigations have shown that in the pathogenesis of COVID-19 infection, oxidative stress (an imbalance between the production and accumulation of cellular reactive oxygen species (ROS) and antioxidant defense) plays a significant role, that may lead to DNA mutations, injury to the mitochondrial respiratory chain, modifications of membrane permeability, and inactivation of the antioxidant defense systems [24,25]. After a viral infection, the body may experience prolonged inflammation, reduced antioxidant defense, and increased oxidative stress. This can trigger long-lasting anti-inflammatory processes, reducing the inflammatory state, restoring immune and oxidative balance, and preventing multiple organ dysfunction. If this compensatory reaction is insufficient, oxidative stress and inflammation usually reinforce each other, contributing to the systemic hyperinflammatory state, which has a wide variety of organ involvement and causes many symptoms, known as post-COVID-19 symptoms. Although studies examining the pathophysiology of the post-COVID-19 syndrome are still relatively few, there is growing evidence that this is a complex and multifactorial syndrome involving virus-specific pathophysiological variations that include many mechanisms, specifically oxidative stress, immune dysfunction, and persistent inflammation [23-25]. In this regard, it is important to assess the contribution of inflammatory and oxidative processes to cellular and tissue damage mechanisms during various post-COVID-19 complications.

According to the results of our studies. level of TAA in the blood serum of patients with VMR (groups I, II) was lower than the blood serum TAA level in healthy volunteers, this decrease was especially significant in patients with VMR developed about 6 months after COVID-19 infection (66% compared to control); these data indicate that oxidative stress in patients with VMR earlier exposed to COVID-19 infection is especially high and its important role in the pathogenesis of post-COVID-19 VMR. The intensive release of oxygen free radicals can cause epithelial damage and induce both the lower and nasal airway hyperresponsiveness [26], contributing to the release of histamine and the development of eosinophilic inflammation in patients earlier exposed to COVID-19 infection.

At the same time, the level of NO in nasal smears of patients with VMR developed after more than 6 months of COVID-19 infection (group I) decreased (was 69% of the level in healthy volunteers) and in patients with VMR, who did not undergo COVID-19 (group II) importantly increased (was 189% of the level in healthy volunteers) in comparison to control level. Nitric oxide (NO) is an important mediator of the various biological processes, which participate in managing the body's immune and inflammatory responses [27-29]. All three isoforms of NO-synthase (NOS) (constitutive - endothelial (eNOS) and neuronal (nNOS), and inducible (iNOS)) are presented in the human nasal mucosa [30]. The majority of NOS in the human nasal airway is associated with the nasal epithelium. Nitric oxide can act as a scavenger of oxygen-free radicals, including superoxide [30]. Therefore, the production of basal levels of NO, by the epithelium, could represent a defensive mechanism and decrease the susceptibility of the epithelium to oxidative damage, resulting in hyperresponsiveness [30].

In a hyper-inflammation state, oxidative stress conditions increase iNOS expression and a rise in NO production is possible. Excess NO readily reacts with the superoxide anion to form cytotoxic peroxynitrite; this induces epithelial cell damage, and nasal airway hyperresponsiveness and increases the severity of VMR. The clinical studies confirm that the NO content in the upper and lower respiratory tract is a validated marker of airway inflammation [26].

Therefore, a basal level of NO production may be protective against airway hyperresponsiveness, excessive NO release, possibly mediated by an upregulation of iNOS during chronic inflammation, may be destructive and cause airway hyperresponsiveness. It is established that the nasal NO level is significantly higher in patients with allergic rhinitis compared to healthy people, while in patients with nonallergic VMR, it was significantly lower (especially in patients with VMR who showed eosinophilia in nasal swabs) [29]. Nasal NO can be identified as a diagnostic marker of patients previously exposed to COVID-19 infection and without it.

Based on the results of the study, we can conclude that the pathogenesis of VMR of a patient previously exposed to COVID-19 infection is characterized by especially high oxidative stress intensity, inducing depletion of TAA in the body, oxidative degradation of NO, lowering of nasal NO

content, causing the abolishment of its protective ability against airway hyperresponsiveness and development the chronic eosinophilic inflammation.

For VMR treatment, we used local intranasal antihistamine spray, reducing the effects of the inflammatory mediators (bradykinin, serotonin, histamine, leukotrienes) in the body.

The results of our study indicate a positive effect of the treatment with intranasal antihistamine spray in patients with VMR (groups I and II). At the same time, it should be noted that positive treatment results are detected faster in patients with VMR who have not undergone COVID-19 infection (group II). These patients showed an improvement in subjective and objective parameters already on the 5th day of treatment - subjective indicators sharply decreased in 64% of patients, the dynamics of objective indicators were positive and on day 10 of the treatment, their normalization was observed in 78% of patients. In patients with VMR who had COVID-19 at least 6 months ago (group I) on the 5th day of treatment, positive dynamics were detected in 52%, and on day 10 - in 62% of patients.

After the treatment in patients of both studied groups, TAA increased (especially in group I), and the level of NO changed towards the control insights (that indicates the decrease of oxidative degradation of nitric oxide and restoring its protective effect against airway hyperresponsiveness}. Accordingly, at the end of the treatment mean eosinophils, lymphocytes, and neutrophils counts in nasal smears of patients with VMR decreased significantly and in group II approached the control level, however, in patients with VMR previously exposed to COVID-19 infection (group I) still importantly exceeded the control level.

Based on the results of our studies, the proposed treatment regimen with the local intranasal antihistamine spray can be recommended for patients with vasomotor rhinitis, both with and without COVID-19 infection. The study results indicate that patients with VMR who had previous COVID-19 infection may require an extended treatment course.

Conclusion.

In patients previously exposed to COVID-19, VMR infection intensity of the oxidative stress and depletion of nasal NO were especially high, causing the abolishment of protective ability, chronic eosinophilic inflammation, and airway hyperresponsiveness. intranasal antihistamine spray is effective for VMR treatment in groups I and II. In patients with VMR who previously had COVID-19 infection, it is necessary to increase the treatment course duration.

Disclosure.

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