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Эпидемиология хронических индуцированных крапивниц в городе Москве

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АННОТАЦИЯ

Обоснование. Хронические индуцированные формы крапивницы — группа заболеваний, характеризующаяся развитием уртикарных высыпаний и/или ангиоотёков в течение 6 и более недель в ответ на воздействие специфических триггеров. По данным мировой научной литературы, встречаемость хронических индуцированных форм крапивницы достаточно высока и составляет 0,5% общей популяции и примерно 20–30% всех хронических крапивниц. Статистических данных о распространённости физических форм крапивницы в Российской Федерации нет.

Цель — оценка эпидемиологии хронических индуцированных крапивниц в рамках популяции одного региона.

Материалы и методы. Анализ осуществлялся посредством подсчёта количества уникальных случаев обращений взрослого населения по поводу данной патологии в амбулаторных формах Единой медицинской информационно-аналитической системы (ЕМИАС) г. Москвы с 2017 по 2021 г., включая поиск по ключевым словам.

Результаты. Распространённость хронических индуцированных форм крапивницы в Москве коррелирует с опубликованными международными эпидемиологическими данными. Среди обратившихся по поводу хронических индуцированных форм крапивницы преобладали женщины (74,2%), медиана возраста составила 43,0 года (37 лет у мужчин и 46,4 года у женщин). Из всех верифицированных случаев хронических индуцированных форм крапивницы самым распространённым типом является дермографическая крапивница (11,12%), далее следуют контактная (5,36%), холинергическая (2,28%), холодовая (1,92%), замедленная крапивница от давления (0,36%), вибрационная (0,11%), аквагенная (0,1%) и тепловая (0,08%) формы. Показатели хронических индуцированных форм крапивницы в Москве высоки и так же, как и в мировой практике, имеют значимую тенденцию к росту. Необходимо внедрение провокационного тестирования для верификации диагноза, использование валидизированных опросников и систематического наблюдения пациентов с хроническими индуцированными формами крапивницы.

Заключение. Таким образом, необходимо дальнейшее изучение данной когорты пациентов с целью верификации диагноза, оценки тяжести течения хронических индуцированных форм крапивницы, коморбидных заболеваний и ответа на проводимую терапию.

Ключевые слова: хроническая индуцированная крапивница; эпидемиология; провокационное тестирование.

Как цитировать

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Epidemiology of chronic inducible urticaria in Moscow

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ABSTRACT

BACKGROUND: Chronic inducible urticaria is a group of diseases that is characterized by the development of wheals, angioedema, or both in response to specific triggers for ≥ 6 weeks. According to global scientific international literature, the occurrence of chronic inducible urticaria is 0.5% in the general population and approximately 20%–30% in all chronic urticarias. The prevalence of chronic inducible urticaria has no statistical data in the Russian Federation.

AIM: This study aimed to evaluate the region-specific epidemiology of different forms of chronic inducible urticaria.

MATERIALS AND METHODS: The analysis is based on the number of unique cases extracted from the medical care records in the adults' segment of the digital platform United medical information and analytical system (UMIAS) (outpatient forms) in Moscow from 2017 to 2021, including keyword search.

RESULTS: This study indicated that the prevalence of chronic inducible urticaria in Moscow is correlated with published global epidemiological data. Among patients with chronic inducible urticarial, females predominate (74.2%), and the median age was 43.8 years (37 years in males and 46.4 in females). The most common form in all verified cases of chronic inducible urticaria is symptomatic dermographism (11.12%), followed by contact urticaria (5.36%), cholinergic urticaria (2.28%), cold urticaria (1.92%), delayed pressure urticaria (0.36%), vibratory urticaria (0.11%), aquagenic urticaria (0.1%), and heat urticaria (0.08%). Chronic inducible urticaria rates in Moscow are high, which increase as in global practice. This research has limitations, including the lack of ubiquitous implementation of standard protocols of provocation testing in outpatient units and the low percentage of using validated questionnaires in the routine management of patients with chronic inducible urticaria.

CONCLUSIONS: Further studies dedicated to this topic are greatly necessary to answer a wide spectrum of questions, including the diagnosis process and evaluation of the severity of chronic inducible urticaria, comorbid conditions, and optimization of the treatment protocols adapted for the particular phenotype.

Keywords: chronic inducible urticaria; epidemiology; provocation testing.

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BACKGROUND

Chronic inducible urticaria (CIndU) is characterized by the appearance of urticarial elements and/or angioedema lasting ≥ 6 weeks in response to specific triggers [1–3]. Depending on the nature of the trigger, CIndU can be caused by physical factors (cold, heat, solar, vibratory, delayed pressure urticaria, symptomatic dermatographism) and non-physical factors (cholinergic exposure, aquagenic, or contact) [1, 3, 4].

As per the existing literature, the incidence of CIndU is quite high, affecting about 0.5% of the general population and contributing to approximately 20%–30% of all cases of chronic urticaria [4, 5]. The most common type of CIndU is symptomatic dermatographism (10% of all chronic urticarias) with a reported prevalence of 2%–5% in the general population [6]. Cold urticaria, on the other hand, is responsible for about 5%–30% of all chronic urticarial cases while its incidence in the general population is only 0.05%; in countries with cold climates, these measures are even higher [7–9]. Regarding non-physical factors, cholinergic urticaria is found in 11.2% of cases, more often between the ages 26–28 years (up to 20% of patients) [10]. Other rare forms of CIndU include solar (0.5%), thermal urticaria (0.2%), and vibratory angioedema (0.1%) [11].

The majority of studies have described that the peak incidence of CIndU is seen in young to middle-aged people (in the 2nd–4th decade of life) [10, 12]. In general, CIndU is characterized by a longer duration of the disease and lower chances of spontaneous remissions within one year in comparison with chronic spontaneous urticaria [13, 14].

Curto-Barredo et al. [15] studied various phenotypes of chronic urticaria and stated that CIndUs are characterized by a lower incidence of concomitant autoimmune diseases and angioedema. In particular, the cold and cholinergic forms are characterized by a high proportion of systemic reactions, especially following massive exposure to the causative trigger, such as being immersed in cold water or prolonged intraoperative time for patients with cold urticaria and increased physical activity with intense sweating in patients with cholinergic urticaria [16, 17]. Furthermore, the comorbid occurrence of chronic spontaneous urticaria and CIndU is observed in an average of one-third of all cases of chronic urticaria [13, 18]. Notably, Sánchez et al. [19] described a sizeable 76.9% incidence of CIndU with chronic spontaneous urticaria. Nevertheless, most authors consider the presence of CIndU in a patient with chronic spontaneous urticaria to be a predictor of a more severe and prolonged course of the disease [20]. Cases of several CIndUs coexisting in one patient have also been described; however, the existence of such combinations has not been corroborated by large-scale randomized controlled studies [20–24].

The pathogenesis of the development of symptoms in CIndU is yet to be comprehended. It is known that there is a definite progression from activation to degranulation of mast cells, followed by the release of histamine and other pro-inflammatory mediators [25] which leads to the symptoms.

However, it is unclear whether skin mast cells are activated by a physical trigger or by an increase in body temperature.

To ascertain a diagnosis of CIndU, the patient's medical history, confirmatory photographs of the skin, and results of provocation testing are used [26]. Provocation tests help to determine a specific trigger's threshold which can elicit the urticarial reaction to evaluate the effectiveness of drug therapy and prescribe custom-tailored recommendations to the patient [27, 28].

The treatment for CIndU is primarily aimed at limiting contact with the trigger, which is not always achievable in real life. The first line of drug therapy comprises non-sedative H1-histamine receptor antagonists which, at a standard dose, allow control over the disease symptoms in an average of 20%–30% of patients with CIndU [5]. Doubling or quadrupling the dose of antihistamines is reported to slightly increase the success of drug therapy [29, 30]. However, some studies have shown that this therapy is less effective in patients with a comorbid course of CIndU and chronic spontaneous urticaria [28, 31]. Omalizumab can be used as off-label therapy or in patients with concomitant chronic spontaneous urticaria. Several clinical studies have shown that omalizumab therapy may be effective in patients who do not respond to antihistamine treatment [32–36]; however, its use is limited by the lack of official guidelines for its clinical use in CIndU.

Patients with CIndU are commonly young age individuals with a significant history of prolonged urticarial symptoms, have a high risk of anaphylaxis, and often report a decrease in the quality of life and non-responsiveness to treatment [10, 12–14, 16, 17, 20]. Therefore, there is a need to explore CIndU, focusing on its epidemiology, pathogenesis, comorbid pathologies, diagnostic algorithms, the effectiveness of therapy, and reasons for the failure of pharmacological treatment. Accordingly, **this study aimed** to determine the epidemiology of inducible urticaria in the adult population from the outpatient forms of the UMIAS (United Medical Information Analysis System of Moscow) using a keyword search.

MATERIALS AND METHODS

Study design

A retrospective cross-sectional analysis of the outpatient card data from the Moscow UMIAS from 2017 to 2021 was carried out to determine the unique number of adult clinical encounters of chronic urticaria.

Eligibility criteria

All cases of a medical encounter for chronic urticaria (code L50 per the International Statistical Classification of Diseases and Related Health Problems – tenth revision, ICD-10) or containing the following keywords and phrases: “induced,” “cold,” “dermatographic,” “delayed pressure urticaria,” “solar,” “cholinergic,” “thermal,” “aquagenic,” “vibratory,” or “contact urticaria” were included.

To calculate the indicator “medical encounter for this disease,” we used settings that allowed the selection of cases based on the results of physical examination done by one of the doctors (examination by a general practitioner, allergist-immunologist, pediatrician, surgeon, or a dermatovenereologist) where the L50.8 ICD-10 code was indicated without taking into account the type of diagnosis and results of examinations by other specialists and discharge summaries, where diagnosis type was indicated as “Primary,” “Complication of the underlying disease,” or “Concurrent.”

The aforementioned specialists were selected due to the keywords used in the diagnoses description (in the results of the examination) of the cases in which the type of diagnosis for urticaria is not indicated as “Primary,” “Complication of the underlying disease,” or “Concurrent.”

Data analysis

The sample size was not previously calculated. The number of unique encounter cases of chronic urticaria was calculated as the number of unique patients who presented at least once with urticaria in each study year.

The number of male/female patients presenting for CIndU and the age of the presenting patients were calculated as indicators of the number of unique patients who presented at least once for urticaria in the study year.

To compute the indicator “percentage of the total number of cases in patients with CIndU,” the total number of encounters in the study year, and not the number of encounters for the entire observation period, was used.

To determine the number of patients in the categories “concomitant allergopathology” and “other concomitant

diseases,” the number of cases with at least one of the concomitant disease codes in patients with inducible urticarias was used.

A specialized statistical software package was not used for the calculation.

RESULTS

Between January 2017 and December 2021, 127,847 people over the age of 18 years were diagnosed with chronic urticaria (L50 according to ICD-10) and applied for outpatient care at medical organizations of the Moscow Healthcare Department. Of these, 17,715 (13.8%) were diagnosed with CIndU (L50.2, L50.3, L50.4, L50.5, L50.6, and L50.8 according to ICD-10). A majority of these patients with CIndU (74.2%) were females. The patients with CIndU applying for medical help for this disease had a median age of 43 years (range: 18–99 years; median age for males = 37 years, for females = 46.4 years).

In 77.32% of cases, the trigger for the appearance of rashes in CIndU was not determined since provocation testing was not performed. In cases where the trigger was identified, the most common trigger was dermographic ($n=1948$, 11.12%), followed by contact ($n=950$, 5.36%), cholinergic ($n=403$, 2.28%), cold ($n=340$, 1.92%), delayed pressure ($n=64$, 0.36%), vibratory ($n=20$, 0.11%), aquagenic ($n=19$, 0.1%), and thermal ($n=14$, 0.08%). Figure 1 illustrates the prevalence of various forms of induced urticaria with respect to all verified disease cases – dermographic urticaria (50%), contact (25%), cholinergic (11%), cold (9%), delayed pressure (2%), vibratory (1%), aquagenic (1%), and thermal (1%).

Among patients with CIndU, the following concomitant allergic diseases were noted – allergic rhinitis ($n=720$, 4.06%), bronchial asthma ($n=716$, 4.04%), atopic dermatitis ($n=103$, 0.32%), and allergic conjunctivitis ($n=29$, 0.17%) (Figure 2).

A combination of several comorbidities was also studied, including Th2-associated and autoimmune diseases, which were previously considered to be risk factors for the protracted course of chronic spontaneous urticaria in patients with CIndU. Diseases of the gastrointestinal tract (gastroesophageal reflux disease, eosinophilic esophagitis) were registered in 14 (0.08%) patients, endocrine diseases (chronic autoimmune thyroiditis, type 1 diabetes mellitus) in 14 (0.08%) patients, autoimmune diseases (vitiligo, Sjogren’s syndrome, ankylosing spondylitis, scleroderma) in 16 (0.09%) patients, diseases of upper respiratory tract (chronic rhinosinusitis with nasal polyposis) in 11 (0.06%) patients, and hematological diseases (B12-deficiency anemia) in 34 (0.19%) patients (Figure 3).

DISCUSSION

We found that the most common type of CIndU in Moscow was dermographic urticaria, which correlates with the global incidence of this disease. Furthermore, cold urticaria is the second most common form of CIndU worldwide, whereas,

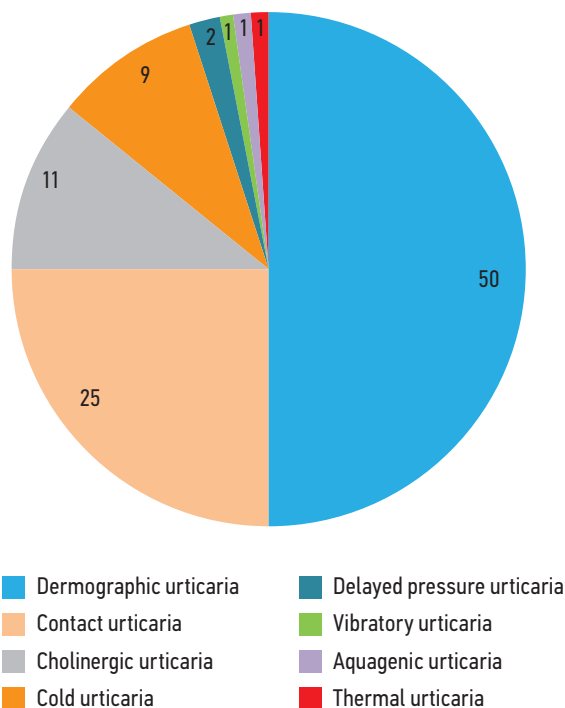


Fig. 1. Correlation of the incidence of different chronic inducible urticaria types (in %).

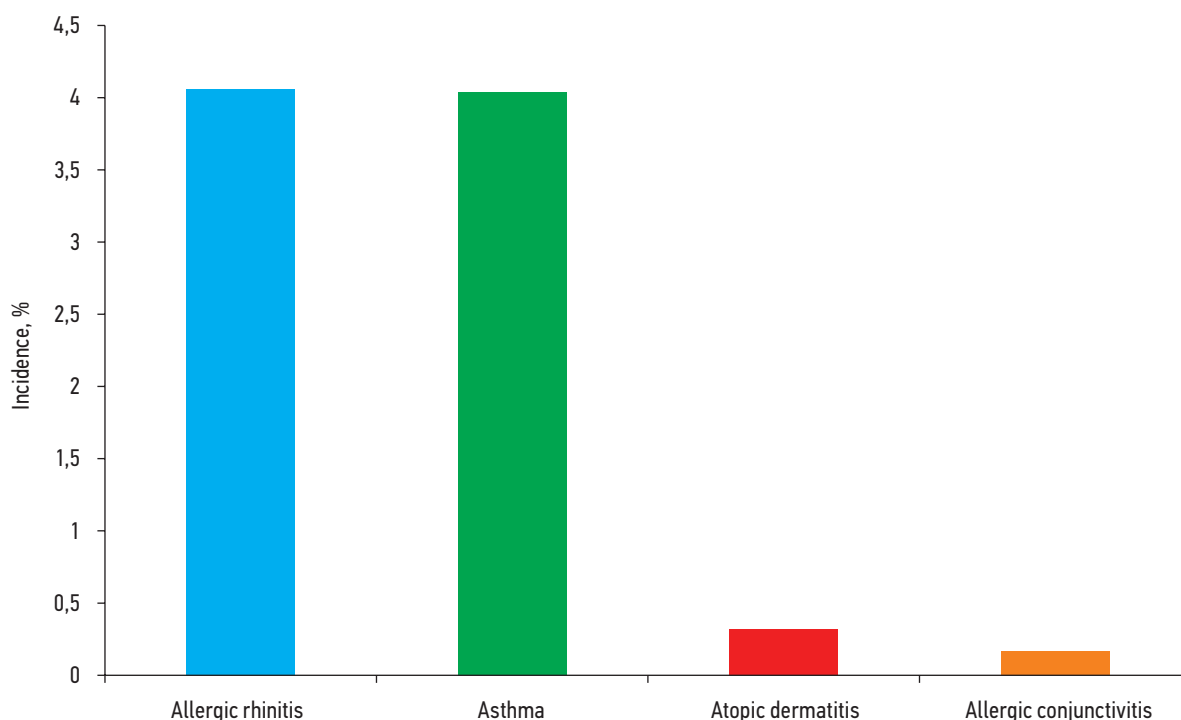


Fig. 2. Incidence of atopic diseases in patients with chronic inducible urticaria.

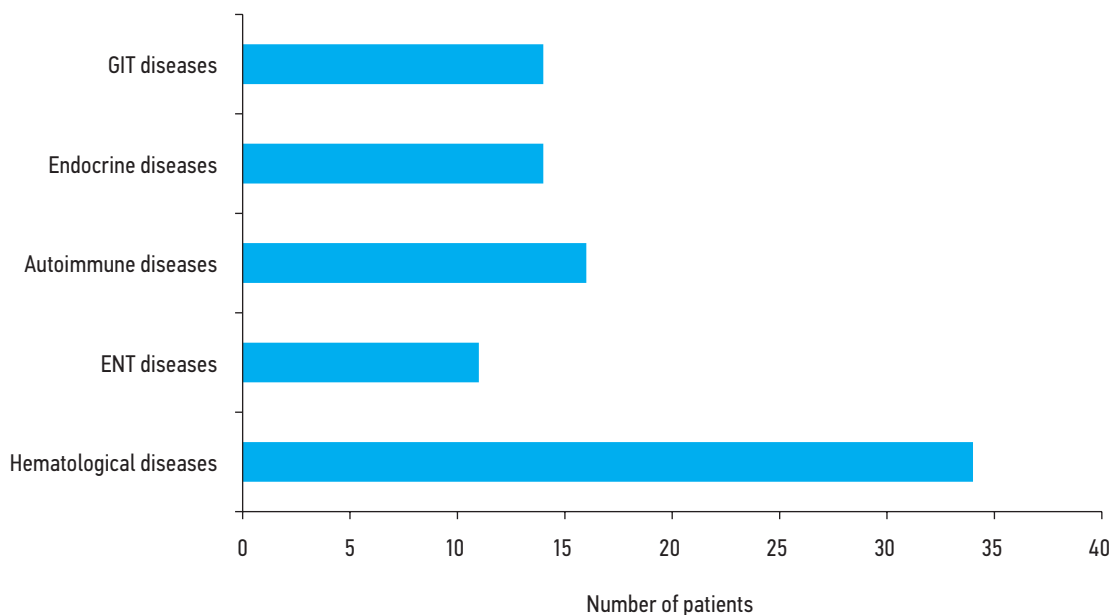


Fig. 3. Incidence of comorbidities in patients with chronic inducible urticaria.

Note: GIT: gastrointestinal tract; ENT: otorhinolaryngological (ear, nose, throat) diseases.

in Moscow, this variety was the fourth most commonly diagnosed form of inducible urticaria. This considerable difference may have occurred due to low clinical suspicion of this pathology in primary care specialists practicing in Moscow. For the same reasons, i.e., the lack of awareness about different types of CIndU in primary care professionals

as well as irregularity in the use of provocation tests, contact urticaria ranks so high in this study.

It can be reasonably presumed that the frequency distribution of different CIndU types may change after provocation testing and diagnosis verification. However, dermatographic urticaria may still be the most prevalent type

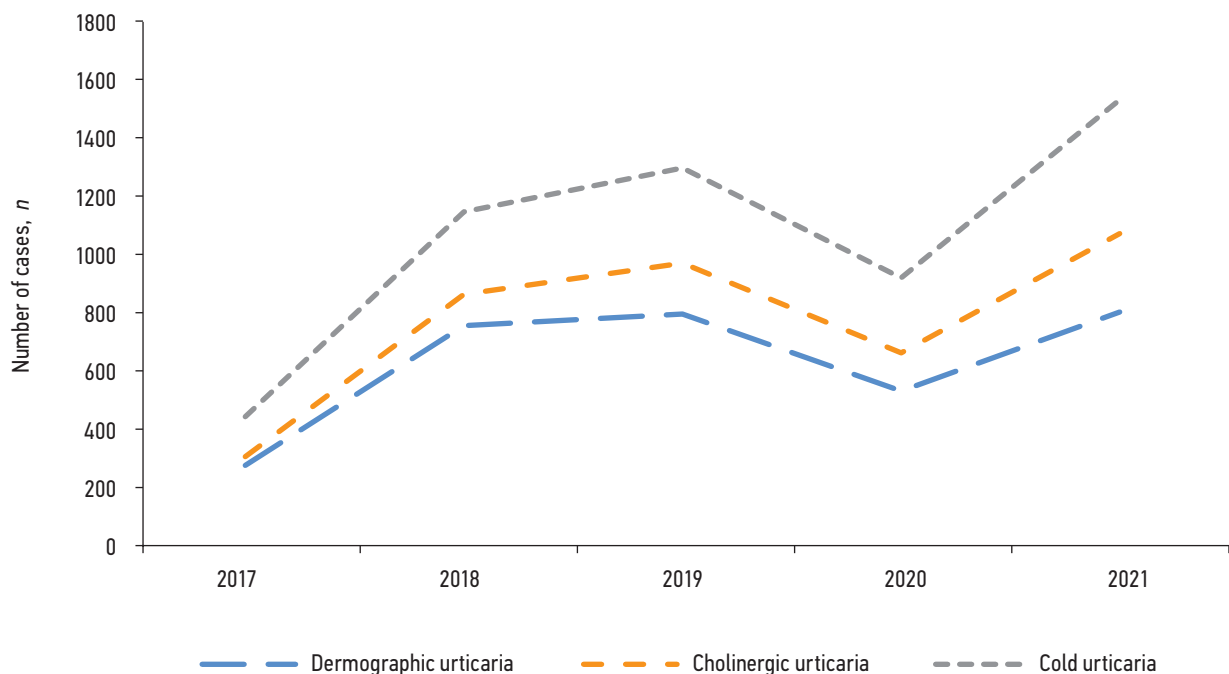


Fig. 4. Increase in the incidence of outpatient visits by patients with cholinergic urticaria, cold urticaria, and dermatographic urticaria.

since it can be easily diagnosed using a common testing procedure (stroke test) which can be carried out by doctors even outside of specialized center conditions. It is noteworthy that from 2017 to 2021, there was a several-fold increase in the number of outpatient visits not only for patients with cold urticaria but also for other CIndU types despite the coronavirus pandemic of 2020 which significantly limited the possibilities of outpatient care. This trend of an increased number of chronic urticaria cases may not only be attributed to an actual increase in disease incidence but also to the efforts of the UCARE¹ centers. These centers execute active awareness campaigns toward the popularization and implementation of CIndU study protocols into clinical practice to increase the clinical suspicion of outpatient specialists and amplify the percentage of verified diagnoses (Figures 4 and 5).

In addition, the findings of greater prevalence of CIndU in the female gender as well as the median age of onset in the 3rd–4th decade of life observed in our study correlate with the existing epidemiological statistics on this disease. Moreover, a low prevalence of atopic diseases in patients with CIndU indicates that the pathogenesis of this disease may involve not only ‘true allergic’ immediate hypersensitivity reactions, but also autoimmune and auto-allergic mechanisms in which nonspecific activation of mast cells and basophils occurs.

Study limitations

Data regarding provocation testing was not available for all clinical encounters of chronic urticaria. Even though this method is currently the gold standard not only for diagnosis

verification but also for determining the management plan and disease prognosis, the diagnosis of CIndU was often made by primary care specialists either empirically or based on clinical and anamnestic data. For definite differential diagnosis of this pool of patients, proactive observation and standardized methods of provocation testing are required.

CONCLUSION

CIndU is highly prevalent in Moscow and continues to have a significant upward trend, which is consistent with the epidemiological data for the world. However, the generalizability of our study results was limited by a lack of universal protocol for provocation testing, the impracticality of conducting certain provocation tests in outpatient settings, the low percentage of validated questionnaires used, and inconsistent observation of patients with CIndU. Thus, further studies of this patient cohort are necessary to develop criteria for verifying the diagnosis, assessing the severity of CIndU and comorbid diseases, and estimating the response to ongoing therapy.

ADDITIONAL INFORMATION

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Authors’ contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval

¹ UCARE-center — Urticaria Centers of Reference and Excellence.

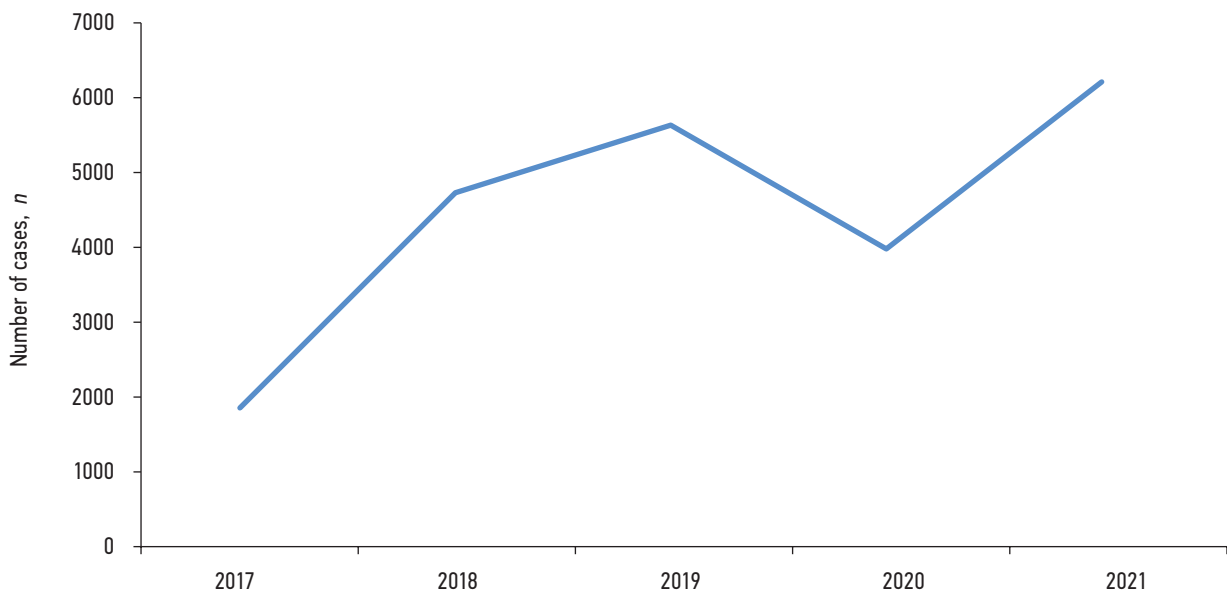


Fig. 5. Increase in the incidence of outpatient visits by patients with delayed pressure urticaria.

of the version to be published and agree to be accountable for all aspects of the work. D.S. Fomina — a literature review, a literature collection and analysis, writing an article, editing of the article; N.P. Maltseva, S.A. Serdotetskova — a literature review, a literature collection and analysis, data analysis, writing an article, editing of the article; I.V. Danilycheva — a literature

review, a literature collection and analysis, editing of the article; M.S. Lebedkina, V.I. Mikhaylova — data analysis, writing an article; E.V. Kovalkova — a literature review, a literature collection and analysis, data analysis; N.S. Chikunov — preparation data for further analysis and hypothesis testing, A.V. Karaulov, M.A. Lysenko — oversaw the study.

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