DOI: https://doi.org/10.36691/RJA1516

Наследственный ангиоотёк с дефицитом С1-ингибитора: ретроспективное исследование 194 пациентов

И.А. Манто[1], Е.А. Латышева[1, 2], Д.О. Тимошенко[1], Ю.А. Горностаева[1], А.М. Костинова[1], Е.Н. Медуницына[1, 3], Т.Н. Мясникова[1], Т.С. Романова[1], Н.Х. Сетдикова[1, 3], Е.А. Фролов[1], О.В. Шубина[1], Т.В. Латышева[1, 3]

[1] Государственный научный центр «Институт иммунологии» Федерального медико-биологического агентства, Москва, Российская Федерация
[2] Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, Москва, Российская Федерация
[3] Московский государственный медико-стоматологический университет имени А.И. Евдокимова, Москва, Российская Федерация

АННОТАЦИЯ

Обоснование. Наследственный ангиоотёк с дефицитом С1-ингибитора — редкое заболевание, вызванное дефицитом и/или снижением функциональной активности С1-ингибитора. Основным симптомом заболевания являются рецидивирующие ангиоотёки различной локализации, которые могут приводить к временной утрате трудоспособности и даже смерти.

Цель — изучить особенности клинического течения заболевания у пациентов с наследственным ангиоотёком из регистра ФГБУ ГНЦ «Институт иммунологии» ФМБА России; выявить предикторы жизнеугрожающих ангиоотёков и потребности в долгосрочной профилактике; сравнить особенности течения заболевания в разных группах пациентов.

Материалы и методы. Из регистра ФГБУ ГНЦ «Институт иммунологии» ФМБА России для участия в ретроспективном описательном исследовании отобраны данные 194 пациентов, страдающих наследственным ангиоотёком с дефицитом С1-ингибитора, из 124 неродственных семей. Диагноз подтверждён в соответствии с принятыми стандартами диагностики.

Результаты. Среди отобранной для анализа когорты пациентов из России преобладали женщины — 70% против 30% мужчин. Средний возраст пациентов — 35±17 лет. У 89% участников диагностирован наследственный ангиоотёк I типа, у 11% — наследственный ангиоотёк II типа. Средний возраст появления первых симптомов — 11±9 лет. У 98% пациентов был хотя бы один периферический ангиоотёк, у 86% — абдоминальная атака, у 86% — ангиоотёк лица, у 49% — ангиоотёк гортани. Средняя задержка в постановке диагноза — 17,5±11,24 года. Чем старше пациент, тем чаще встречаются отёки гортани (p <0,001), отёки лица и шеи (p <0,001), абдоминальные атаки (p=0,031). Не выявлено значимых различий по клиническим параметрам между мужчинами и женщинами.

Заключение. В России существует проблема длительной задержки постановки диагноза наследственного ангиоотёка с дефицитом С1-ингибитора. В результате проведённого исследования идентифицированы факторы риска развития жизнеугрожающих ангиоотёков: возраст пациента (чем старше пациент, тем выше риск), наличие ангиоотёков лица и шеи в анамнезе. Кроме того, выявлен ряд настораживающих критериев наследственного ангиоотёка с дефицитом С1-ингибитора: наличие семейного анамнеза, сочетание рецидивирующих периферических ангиоотёков и абдоминальных атак, дебют ангиоотёков и/или абдоминальных атак в раннем детском возрасте. Наличие таких критериев позволит ускорить диагностику заболевания.

Ключевые слова: наследственный ангиоотёк; НАО; ангиоотёк; С1-ингибитор; брадикинин.

Как цитировать

Манто И.А., Латышева Е.А., Тимошенко Д.О., Горностаева Ю.А., Костинова А.М., Медуницына Е.Н., Мясникова Т.Н., Романова Т.С., Сетдикова Н.Х., Фролов Е.А., Шубина О.В., Латышева Т.В. Наследственный ангиоотёк с дефицитом С1-ингибитора: ретроспективное исследование 194 пациентов // *Российский аллергологический журнал*. 2022. Т. 19, № 1. С. 53–66. DOI: https://doi.org/10.36691/RJA1516

Рукопись получена: 25.01.2022 **Рукопись одобрена:** 24.02.2022 **Опубликована:** 11.03.2022

DOI: https://doi.org/10.36691/RJA1516

Hereditary angioedema with C1-inhibitor deficiency: a retrospective study of 194 patients

Irina A. Manto[1], Elena A. Latysheva[1, 2], Daria O. Timoshenko[1], Yulia A. Gornostaeva[1], Aristitsa M. Kostinova[1], Ekaterina N. Medunitsyna[1, 3], Tatyana N. Myasnikova[1], Tatyana S. Romanova[1], Nailya Kh. Setdikova[1, 3], Evgeniy A. Frolov[1], Olga V. Shubina[1], Tatiana V. Latysheva[1, 3]

[1] National Research Center — Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russian Federation
[2] Pirogov Russian National Research Medical University, Moscow, Russian Federation
[3] Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russian Federation

ABSTRACT

BACKGROUND: Hereditary angioedema due to C1-inhibitor deficiency is a rare disease caused by deficiency and/or low functional activity of C1-inhibitor. The main symptom of hereditary angioedema is recurrent angioedema in various localizations, which can lead to temporary incapacity or even death.

AIM: To study the features of the clinical course of the disease in patients with hereditary angioedema from the registry of the National Research Center (NRC) "Institute of Immunology" of the FMBA of Russia, identify the predictors of life-threatening angioedema and the need for long-term therapy, and compare the features of the course of the disease in different groups of patients.

MATERIALS AND METHODS: A total of 194 patients from NRC Institute of Immunology FMBA of Russia registry from 124 unrelated families with a diagnosis of hereditary angioedema with C1-inhibitor deficiency, confirmed in accordance with accepted diagnostic standards, were enrolled in the retrospective descriptive study.

RESULTS: Overall, 194 patients were included in the analysis (70% female and 30% male). The mean age of patients was 35±17 years. Moreover, 89% and 11% of patients had hereditary angioedema types I and II, respectively. The mean age of clinical onset was 11±9 years. Ninety-eight percent of participants had a history of at least one episode of peripheral angioedema, 86% experienced abdominal attacks, 86% experienced facial swellings, and 49% experienced laryngeal attacks. The mean diagnostic delay was 17.5±11.24 years. The older the patient is, the more possible laryngeal attacks (p <0.001), facial and neck swellings (p <0.001), and abdominal attacks are (p=0.031). No significant differences in clinical features were noted between men and women.

CONCLUSIONS: There is a problem of a long diagnostic delay of hereditary angioedema in Russia. As a consequence of the study, we have identified a number of warning criteria of hereditary angioedema: the presence of a family history, a combination of recurrent angioedema and abdominal attacks, and the onset of angioedema and/or abdominal attacks in early childhood. The existence of such criteria will make it possible to optimize the diagnosis of hereditary angioedema. Moreover, we have identified the risk factors for the development of life-threatening angioedema: the patient's age (the older the patient, the higher the risk) and a history of angioedema of the face and neck.

Keywords: hereditary angioedema; HAE; angioedema; C1-inhibitor; bradykinin.

To cite this article

Manto IA, Latysheva EA, Timoshenko DO, Gornostaeva YuA, Kostinova AM, Medunitsyna EN, Myasnikova TN, Romanova TS, Setdikova NKh, Frolov EA, Shubina OV, Latysheva TV. Hereditary angioedema with C1-inhibitor deficiency: a retrospective study of 194 patients. *Russian Journal of Allergy.* 2022;19(1):53–66. DOI: https://doi.org/10.36691/RJA1516

Received: 25.01.2022 **Accepted:** 24.02.2022 **Published:** 11.03.2022

BACKGROUND

Hereditary angioedema (HAE) is a rare, potentially life-threatening disease that manifests as swelling of the skin and subcutaneous tissue caused by the accumulation of the mediator bradykinin. This is the key feature that determines the specifics of the pathogenesis, clinical course of the disease, and its treatment.

The prevalence of HAE with C1-inhibitor deficiency (C1-INH) is 1:50,000 [1, 2]. There is an even rarer form of HAE, without C1-INH deficiency, but it is not evaluated in this study.

The pathogenesis of HAE is fundamentally different from that of angioedema (AE) caused by mast cell mediators. The disease develops due to C1-INH deficiency (HAE type I) or decrease in its functional activity (HAE type II) due to a mutation in the *SERPING1* gene (Serpin Family G Member 1), which leads to the accumulation of the mediator bradykinin. In the vast majority of cases, HAE is inherited in an autosomal dominant manner; however, there are isolated reports on autosomal recessive inheritance. Most patients have a family history of the disease; however, in approximately 20–25% of patients, the disease develops due to a newly revealed mutation in the *SERPING1* gene, i.e., there is no family history [3, 4]. The interaction of bradykinin with type 2 bradykinin receptors (B2) leads to vasodilation, an increase in the permeability of the vascular wall with fluid extravasation, which causes the development of edema in various parts of the body [5–8].

Recurrent AE in various parts of the body (peripheral AE, abdominal attacks, AE of the upper airway) is the main clinical symptom of HAE. A characteristic feature of the swelling in HAE is inefficacy of glucocorticoids and antihistamines. These AEs require specific, pathogenesis-based therapy for both prevention and relief. Lack of therapy or suboptimal therapy leads to the development of AE, which can be painful, adversely affect appearance, and lead to temporary disability and death [1, 5, 9, 10].

HAE is a rare disease; therefore, it is extremely important to gain knowledge about it to improve its diagnosis and treatment. To date, several studies that describe the features of the HAE course in patients from different countries have been conducted [11–19], but no analysis of a large sample of Russian patients has been performed. Considering that the clinic of the Institute of Immunology has accumulated extensive experience in managing patients with HAE in Russia, we conducted a study to perform a comprehensive analysis of patients from the Institute of Immunology registry.

Aim: This study aimed to evaluate the demographic and clinical features of the course of HAE in Russian patients; identify predictors of life-threatening AE and the need for long-term prevention; and compare the features of the disease course in different groups of patients (in men and women; in adults and children).

METHODS AND MATERIALS

Study Design

We conducted a single-center, observational, descriptive, retrospective study on a cohort of Russian patients with HAE with C1-INH deficiency.

Eligibility Criteria

The study included 194 patients from 124 unrelated families, who were selected from the registry of the National Research Center Institute of Immunology FMBA of Russia.

The inclusion criterion was a diagnosis of HAE with C1-INH deficiency, confirmed in accordance with the accepted diagnostic standards [1, 20].

The exclusion criteria were HAE without C1-INH deficiency and data in the medical records that did not allow for reliable confirmation of the diagnosis of HAE with C1-INH deficiency.

Study Conditions

The study was conducted in the National Research Center Institute of Immunology FMBA of Russia (Moscow).

Study Duration

Data were collected and analyzed from September 2019 to March 2020.

Description of Medical Intervention

A retrospective analysis of the data was conducted during the study. There was no medical intervention.

Main Study Outcome

We defined important epidemiological characteristics of a cohort of patients with HAE with C1-INH deficiency and determined the clinical characteristics of the study group of patients, including the mean age at the onset of disease, and incidence of AE in various parts of the body, including symptoms. We identified the mean diagnostic delay and also established a correlation between the patient's age and diagnostic delay.

A search was made for predictors of severe HAE with C1-INH deficiency and development of upper airway AE. The factors affecting the decision to prescribe drugs for long-term prophylaxis were analyzed.

Subgroup Analysis

The patients enrolled in the study (n=194) were divided into two groups based on their age: The group of children consisted of 31 patients aged <18 years, while the group of adults included 163 patients aged ⩾18 years.

A descriptive and comparative analysis was conducted in the groups for the following parameters: mean age; number of patients with clinical manifestations of the disease; mean age of documented clinical onset; mean diagnostic delay; incidence of AE in various parts of the body and marginal

erythema; number of patients using drugs for long-term prophylaxis; and mean score on the HAE severity scale proposed by Bygum et al. [21].

All patients enrolled in the study (*n*=194) were divided into two groups by sex: The male group consisted of 59 patients, and the female group consisted of 135 patients. The subgroup analysis was conducted for the same parameters compared with the characteristics of the disease course in children and adults.

Outcome Reporting Methods

We analyzed all outpatient records of patients diagnosed with HAE in the clinic of the Institute of Immunology, which was established in 1991 *(n=228)* [1, 20]. If the patient's data were incomplete or collected more than 2 years ago, the investigator updated the information by interviewing the patient.

To assess the disease severity in patients, the Bygum scale (2011) was used (Table 1).

Ethical Review

The study was approved by the local ethics committee of the National Research Center Institute of Immunology FMBA of Russia (Meeting Minutes No. 3 of March 14, 2016).

Statistical Analysis

A descriptive and comparative statistical analysis of the data was performed using software for statistical data processing, including IBM SPSS Statistics (USA), RStudio (USA), and MS Excel (USA). The results are presented as summary tables and graphs.

Descriptive statistical analysis of the data was performed using parameters, such as arithmetic mean, mode, median, and standard deviation of the sample. Comparative analysis of quantitative data was performed using the Mann–Whitney U test, and qualitative data were analyzed using Pearson's chi-squared test (χ^2) and Fisher's test. Spearman's test was used to assess the correlation between the events. The difference was considered statistically significant at a *P*-value <0.05. Akaike's information criterion (AIC) was used to estimate the prediction error.

Since HAE is an orphan disease and patients with HAE are extremely rare in the general population, it was not possible to precalculate the sample size.

RESULTS

Study Subjects (Participants)

The study included data from a registry of 194 patients with HAE due to C1 inhibitor deficiency, of which 59 were male (30%) and 135 were female (70%). The mean age of patients was 35±17 years (mode, 38 years; median, 34.5 years).

HAE type I was diagnosed in 173 (89%) patients included in the study, while HAE type II in 21 (11%) patients. Thirteen (7%) patients had no clinical manifestations of the disease with a significant decrease in the C1-inhibitor level and/or its functional activity, and all of them were relatives of patients with a confirmed diagnosis of HAE (Table 2).

Most patients (*n*=181) already presented symptoms of the disease upon inclusion in the study, of which 144 (74%) had a family history. In 42 (21%) patients, at least one relative died of manifestations of HAE.

Main Study Results

In 86% of patients, the onset of the disease occurs in the first two decades of life (mean age of clinical onset, 11±9 years). In other patients, the first symptoms of the disease manifested at different times, until the age of 50 years (Fig. 1). The symptoms included isolated peripheral AE in 103 (56.9%) patients; isolated abdominal attacks in 57 (31.5%); and both symptoms in 19 (10.5%). The disease manifested with laryngeal AE in two (1.1%) patients. In 10% of patients, the disease manifested as isolated abdominal attacks in childhood, while the patients had no family history.

Table 1. Bygum (2011) scale for assessing the hereditary angioedema's severity [21]

Sign	Score
Age of clinical onset is 0–5 years	3
Age of clinical onset is 6–10 years	2
Age of clinical onset is 11–20 years	1
Age of clinical onset is >20 years	0
Peripheral angioedema (at least once)	1
Abdominal attack (at least once)	2
Laryngeal angioedema (at least once)	2
Other clinical manifestations	1
Long-term prophylaxis (ever in life)	1

The most common symptom in patients with HAE (98%) was recurrent peripheral AE. The second most common symptom was abdominal attacks, which occurred in approximately 86% of patients, while unjustified surgical interventions were performed in 20% of patients. AE of the soft tissues of the face and neck is a common symptom in our patients (86%). Moreover, 49% of patients had at least one episode of laryngeal AE in their lifetime (4% of patients underwent tracheostomy and/or coniotomy at least once in their lives). Symptoms of marginal erythema were reported only in 17% of cases; 79% of patients required long-term prophylaxis for at least a short period (Table 3).

The mean diagnostic delay (only the data of patients with clinical manifestations were considered) was 17.5±11.24 years, while the mean diagnostic delay was 7.6 years in patients aged < 30 years and 22.86 years in patients aged ⩾30 years. There is a significant correlation between the age and

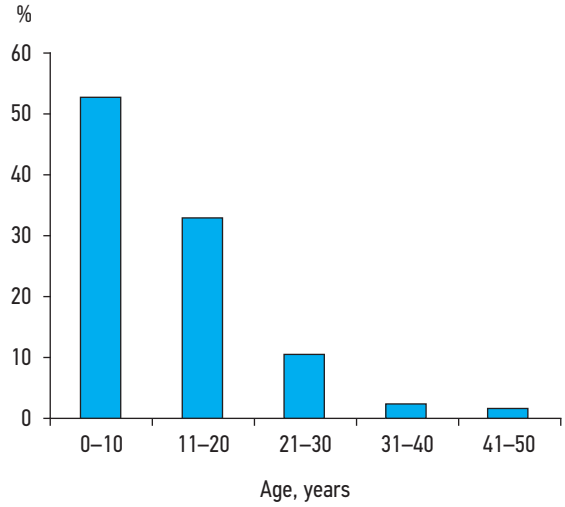

Fig. 1. Age of symptoms onset (*n*=181).

Table 2. Epidemiological data of patients with hereditary angioedema with C1-inhibitor deficiency (*n*=194)

Parameter	Value
Number of patients, *n*	194
Families, *n*	125
Patients at subclinical stage, %	7
Hereditary angioedema type I, %	89
Hereditary angioedema type II, %	11
Men, %	30
Women, %	70
Mean age, years	35±17
Family history, %	74
Death of a relative from laryngeal edema, %	22

Table 3. Most common clinical manifestations (*n*=181)

Sign	Number of patients, *n*	Proportion of patients, %
Peripheral angioedema	177	98
Face and neck angioedema	156	86
Laryngeal angioedema	89	49
Abdominal attacks	156	86
Marginal erythema	31	17
Peripheral angioedema and abdominal attack	152	84
Peripheral angioedema and laryngeal angioedema	87	45
Peripheral angioedema, abdominal attacks and laryngeal angioedema (complete triad of symptoms)	80	41

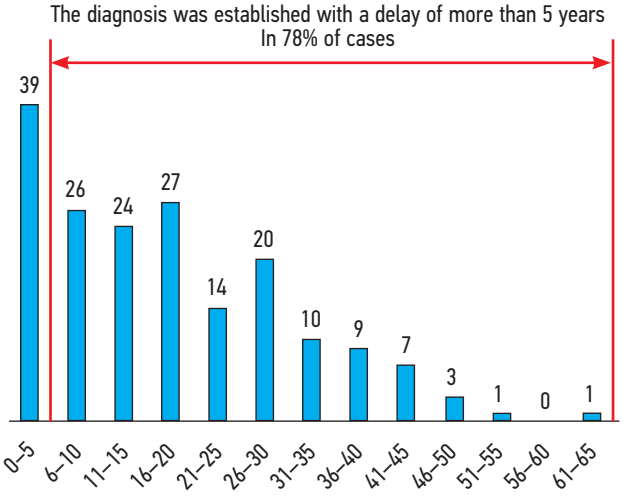

Fig. 2. Diagnostic delay of HAE types I and II (*n*=181).

diagnostic delay (the older the patient, the longer the delay): rS=0.689, p <0.001 (Fig. 2).

To identify predictors of severe HAE, we assessed age as a possible disease-modifying factor. The following pattern was revealed: the older the patient, the more frequent the laryngeal attacks (p <0.001, Mann–Whitney U test), face and neck AE (p <0.001, Mann–Whitney U test), and abdominal attacks (p=0.031, Mann–Whitney U test) (Fig. 3).

Given that the cause of death in patients with HAE is laryngeal AE, we conducted a separate search for possible predictors (other than the patient's age) of the development of AE at this site. In the study on the relationship between laryngeal AE and various demographic and clinical parameters, an additional relationship was found between laryngeal AE and history of face and neck swellings and abdominal attacks (Table 4).

To reduce the probability of obtaining false results due to the effect of age (given that we have found a significant relationship between age and laryngeal AE, face and neck AE, a history of abdominal attacks) and identify which of these parameters are real predictors of AE, we conducted an additional analysis using the AIC. For this, we built a binomial model based on the assumed influencing parameters: age and presence of abdominal attacks and face and neck AE. The analysis found that the effect of abdominal attacks was not statistically significant at the 95% level. Thus, the higher the age, the higher the probability. Moreover, the presence of face and neck AE increased the risk of laryngeal AE.

When stratifying the study group by age, there is a significantly larger number of patients who had at least one episode of laryngeal AE in the older age groups than in the younger groups (p <0.001) (Fig. 4).

We have analyzed the factors affecting the decision to prescribe drugs for long-term prophylaxis. Thus, drugs for long-term prophylaxis were significantly prescribed more often to patients with a history of facial AE (p=0.02), laryngeal AE (p=0.015, Pearson's chi-squared test), abdominal attacks (p=0.012, Pearson's chi-squared test). The mean age of patients who had already used long-term prophylaxis medications for at least a short period (40.1 years) was significantly higher than the mean age of patients who had no such experience (25.1 years) (p <0.001, Mann–Whitney U test).

We compared various aspects of the course of HAE in groups of children and adults (Table 5). Among children, there was a high proportion of asymptomatic disease (35%), only 1% had no clinical manifestations of the disease among adult patients; this difference is statistically significant (p <0.001, Fisher's exact test). The mean age of documented clinical onset in children is significantly lower than that in adults: 4.3 vs. 12.3 years (p <0.001, Mann–Whitney U test). The mean diagnostic delay in children is also significantly lower than that in adults: 3 years vs. 19 years (p <0.001, Mann–Whitney U test).

There was no statistically significant relationship between the age group of patients and history of peripheral AE, face and neck AE, and marginal erythema. However, adult patients are more likely to have a history of laryngeal AE (p <0.001, Fisher's exact test) and abdominal attacks (p=0.09, Fisher's exact test). Only one child had laryngeal AE. Moreover, 85% of adults and 35% of children needed long-term prophylaxis (at least once in their lifetime): this difference is statistically

Table 4. Relationship between upper respiratory tract angioedema and demographic and clinical parameters

Parameter	*p*
Type of hereditary angioedema	0.769[1]
Sex	0.738[1]
History of face and neck angioedema	<0.001[1]
History of abdominal attacks	<0.001[1]
Marginal erythema	0.137[1]
Patient's age	<0.001[2]
Age of clinical onset	0.399[2]

Note: [1] Chi-squared test; [2] Mann–Whitney U test.

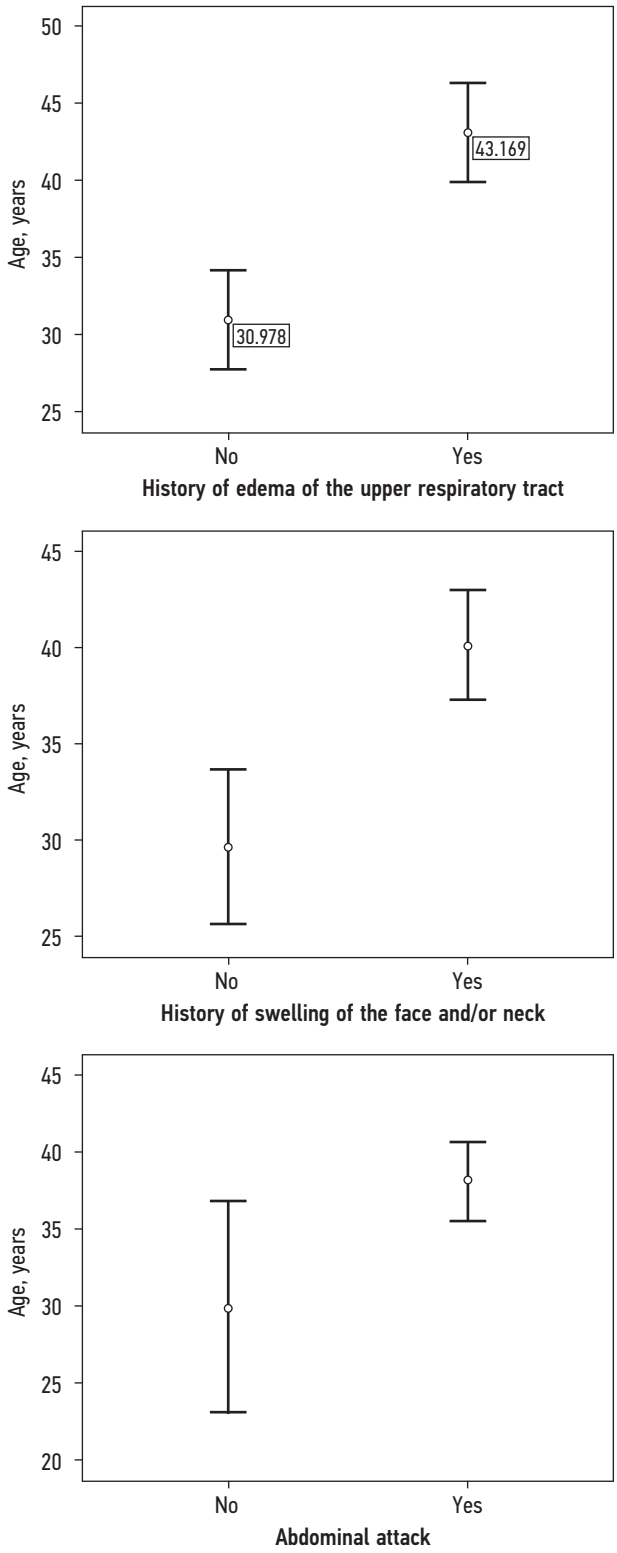

Fig. 3. Dependence of clinical symptoms on age.

significant (p <0.001, Fisher's exact test). The overall severity of the disease (Bygum scale, 2011) ranged from 4 to 10 (mean, 6.0) points in children and from 1 to 10 (mean, 7.1) points in adults. Thus, adult patients have more severe disease compared to children (p=0.05, Mann–Whitney U test) (Table 5).

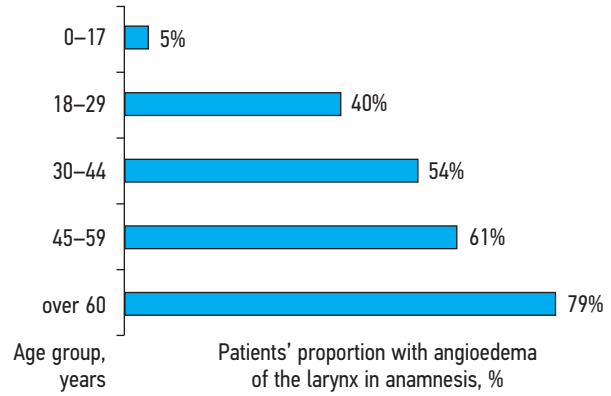

Fig. 4. The presence of laryngeal angioedema in patients in different age groups.

We also compared the features of the HAE course in male and female patients (Table 6). Furthermore, 12% of male patients are asymptomatic, while only 2% of female patients are symptom-free. This difference is only a trend and not statistically significant (p=0.068, Fisher's exact test). The mean age of clinical onset is 10.9 years in male patients and 11.6 years in female patients, which is not a statistically significant difference (p=0.142, Mann–Whitney U test). The mean diagnostic delay in men is significantly lower: 14.3 years vs. 18.9 years in women (p=0.04, Mann–Whitney U test). There was no statistically significant relationship between sex and history of individual clinical symptoms (peripheral AE, face and neck AE, abdominal attacks, laryngeal AE, marginal erythema). In the two study groups, there was approximately the same need for long-term prevention (77% in male patients and 78% in female patients). The overall severity of the disease ranged from 3 to 10 (mean of 7.0) points in men and from 1 to 10 (mean of 7.7) points in females; however, there was no statistically significant difference between the two groups (p=0.851, Mann–Whitney U test).

Adverse Events

Since the study design included only a retrospective data analysis, adverse events were not recorded during the study.

DISCUSSION

Summary of the Main Study Results

The study revealed that patients with HAE are characterized by a family history, combination of recurrent AEs and abdominal attacks, and onset of AEs and/or abdominal attacks in early childhood. Patients with HAE also showed a significant diagnostic delay, with a correlation between the patient's age and diagnostic delay. We established risk factors for life-threatening AEs, such as the patient's age and history of face and neck AEs. In adult patients, the HAE course is significantly more severe than that in children.

Table 5. Comparison of the clinical course of hereditary angioedema with C1-inhibitor deficiency in children and adult groups

Sign	Children	Adults	*p*
Number of patients, *n*	31	163	-
Mean age, years	10.8	40.0	-
Number of patients with clinical manifestations, *n* (%)	20 (65)	161 (99)	<0.001[1]
Mean age of documented clinical onset, years	4.3	12.3	<0.001[2]
Mean diagnostic delay, years	3	19	<0.001[2]
Peripheral angioedema, %	100	98	1.0[1]
Abdominal attacks, %	65	89	0.09[1]
Face and neck angioedema, %	50	73	0.66[1]
Laryngeal angioedema, %	5	55	<0.001[1]
Marginal erythema, %	15	17	1.0[1]
Long-term prophylaxis, %	35	84	<0.001[1]
Mean Bygum scale (2011) score	6	7	0.05[2]

Note: [1] Fisher's exact test; [2] Mann–Whitney U test.

Table 6. Comparison of the clinical course of hereditary angioedema with C1-inhibitor deficiency in male and female groups

Sign	Male patients	Female patients	*p*
Number of patients, *n*	59	135	-
Mean age, years	32.6	36.6	-
Number of patients with clinical manifestations, %	12	2	0.068
Mean age of clinical onset, years	10.9	11.6	0.142
Mean diagnostic delay	14.3	18.9	0.04
Peripheral angioedema, %	98	95	1
Abdominal attack, %	83	86	0.387
Face and neck angioedema, %	65	70	0.372
Laryngeal angioedema, %	50	48	0.887
Marginal erythema, %	12	19	0.205
Long-term prophylaxis, %	77	78	0.662
Mean Bygum scale (2011) score	7.0	7.7	0.851

Discussion

The study provided an opportunity to not only collect data on a quite large population of patients with HAE from the Institute of Immunology registry but also conduct their comprehensive analysis.

Furthermore, 74% of the examined patients had a family history, which is consistent with the data published by our colleagues [12–14]. Moreover, 26% of patients did not have a family history, which indicates that HAE cannot be ruled out in the differential diagnosis of patients with recurrent AEs without a family history.

Since this disease is inherited in an autosomal dominant manner, it was expected that the male-to-female ratio would be approximately the same, as shown in the studies by Xu et al. [17], Kargarsharif et al. [13], and Steiner et al. (approximately 50%/50%) [16]. However, among our patients, the proportion of women (70%) significantly exceeded the proportion of men (30%). A similar female predominance was observed in the Brazilian (women, 67.3%) [11], Turkish (women, 60%) [12], American (women, 78.2%) [19], and French (women, 69.4%) [15] patients with HAE. To date, the reasons for the prevalence

of female patients with HAE remain unknown. A number of assumptions can be put forward:

1) Inheritance had reduced penetrance in male patients.
2) The disease in female patients is more severe than that in male patients, so they seek medical attention more often.
3) The effect of sex hormones, particularly estrogen, plays a role.

The mean age of patients in our cohort was 35 years, which is generally consistent with the data of other researchers [11, 12, 18]. This is the reason that awareness of this condition is important for both pediatricians and adult care practitioners.

HAE is characterized by an early onset in the first two decades of life [22]. We also observed a similar trend among our patients: the clinical onset of the disease occurred before the age of 10 years in more than half of patients (53%) and between 11 and 20 years in another 33% of patients. However, a later onset of the disease does not rule out the possibility of HAE. In our population, the disease manifested between the ages of 21 and 50 years in 14% of patients (Fig. 1), while case reports of the clinical onset of the disease at a later age were also described. Thus, Xu et al. [17] demonstrated that the disease onset in the second and third decades of life is typical for the patient population they studied. The results demonstrate the necessity to raise the awareness on HAE among pediatricians.

Interestingly, we observed a much lower mean age of documented clinical onset of the disease in the group of patients aged <18 years (4.3 years) vs. the adult group (age ⩾18 years) — 12.3 years. A similar trend (6.56 and 14.95, respectively) was demonstrated by Kargarsharif et al. [13]. This may be explained by the fact that, in older patients, early manifestations of HAE were not regarded as symptoms of this disease and therefore were missed. Many younger patients are children of patients with HAE; therefore, awareness of HAE symptoms is higher in these patients. In addition, in older patients, history taking is less accurate. Thus, the age of onset of the disease is often related not to the actual age of first clinical manifestations of HAE in the patient but to the age when these manifestations were recorded. Considering that, in the context of HAE, the age of the first clinical manifestations is often the study subject (the relationship between the age of onset of the first symptoms and overall severity of the HAE course, the effect of the genotype on the age of onset), the data obtained are of great scientific value: it becomes obvious that the current age of the patient should be considered. Otherwise, unreliable results may be obtained.

As for the symptom, the majority of patients at the initial stage of the disease had peripheral AE either as an independent symptom (56.9% of patients) or in combination with abdominal attacks (10.5%). In one-third (31.5%) of patients, the disease began with isolated abdominal attacks, which undoubtedly represents a serious diagnostic problem: it is extremely difficult to suspect the diagnosis of HAE in this case. The data obtained demonstrate the need to raise awareness of HAE among gastroenterologists, since patients with HAE who complained of abdominal attacks may seek medical attention from these doctors in the first place. Moreover, the disease manifested with laryngeal AE in two patients. This fact emphasizes the need to diagnose HAE at the subclinical stage of the disease, since even the first AE in life can become fatal.

The mean diagnostic delay among patients at the Institute of Immunology clinic is 17.5 years (the minimum delay is 0 years; the maximum is 61 years). This parameter is one of the highest in compared with the data of other researchers [11–17]. Such a long interval between the clinical onset of the disease and diagnosis indicates obvious difficulties in the diagnosis in the country. However, a positive trend can be noted: the number of patients under observation is increasing (Fig. 5). Furthermore, the mean diagnostic delay in the group of patients aged <30 years is 7.6 years, which is significantly lower than in the group of patients aged ⩾30 years (22.86 years) (p <0.001). The study findings suggest that the diagnosis of HAE in Russia has improved significantly over the past 10 years. Moreover, we actively examined the relatives of newly diagnosed patients, even if they do not have symptoms of HAE. Therefore, we can expect a reduction in the interval between the clinical onset and diagnosis in the future.

A long delay in making a diagnosis leads to serious consequences: at least one relative died from the clinical manifestations of HAE in 22% of patients; 20% of patients underwent unreasonable surgical intervention (both laparotomy and laparoscopy were considered); 4% underwent one of the manipulations — tracheostomy, coniotomy, and tracheal intubation. Other researchers report a much lower frequency of unreasonable surgical interventions: 5.2, 2.53, and 9% in studies by Alonso et al., Xu et al., and Bouillet et al., respectively [11, 15, 17]. Perhaps this is due to the fact that colleagues did not consider minimally invasive interventions (diagnostic laparoscopy).

We confirmed the previous data that peripheral AE develops in almost all patients with HAE (98%). The second most common symptom is abdominal attacks (86%), which is also

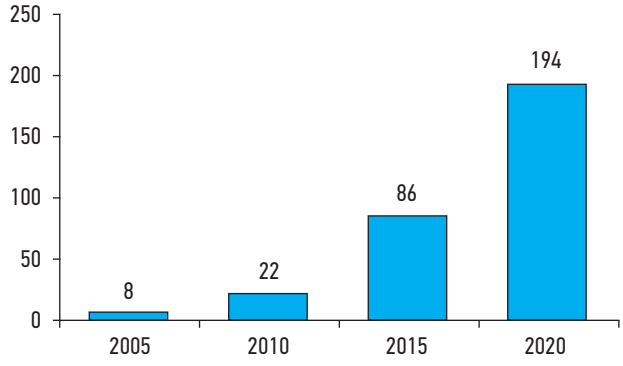

Fig. 5. The dynamics of the increase in the number of patients with hereditary angioedema with C1-inhibitor deficiency, observed at the Institute of Immunology.

consistent with the data obtained by other researchers [11]. Laryngeal AE in the reviewed patient population was somewhat less common than previously described [11–17]. It is extremely important to note that 86% of patients had a combination of clinical manifestations: peripheral AE and abdominal attacks. Similar results were obtained by Danish researchers, who found that 90% of patients had two of the three major symptoms of HAE (peripheral AE, laryngeal AE, abdominal attacks) [23]. Thus, recurrent AE in combination with abdominal attacks of unknown origin is an important warning sign of HAE (along with a family history and poor response to systemic corticosteroids and antihistamines). A complete triad of major clinical symptoms was observed in 44% of our patients, which is also consistent with the data of a researcher from Denmark (49%) [23].

Taking into account that laryngeal AEs in HAE are potentially fatal, a very important objective of our study was to identify predictors of AE of this site. We were able to demonstrate that the risk of laryngeal AE development in a patient increases with age, which may be due to concomitant diseases and their effect on the course of HAE. Moreover, there should be increased alertness to the development of this symptom in patients with face and neck AE.

To date, the clear criteria for prescribing drugs for long-term prophylaxis in HAE have not been defined [24]; therefore, it was very important for us to identify the factors affecting the decision to prescribe long-term prophylaxis in patients with HAE. A history of abdominal attacks and face and laryngeal AEs was identified as such a predictor. The need for long-term prophylaxis increases significantly with age. The study findings can become one of the criteria for prescribing long-term prophylaxis.

The comparison of the characteristics of the disease course in the groups of adults and children showed that the need for long-term prophylaxis is lower in children than in adults. Furthermore, children are much less likely to have such manifestations as abdominal attacks and laryngeal AE. Moreover, the disease in children is characterized by a milder course in general compared to adults when assessed using the Bygum scale (2011), even though the onset is observed much earlier than that in adults. The findings suggest that HAE is milder in childhood. This is supported by the fact that the majority of patients with subclinical HAE are children.

The comparison of the features of the HAE course in male and female patients did not demonstrate significant differences between the two patient groups in either individual clinical parameters or the overall severity of the disease, as assessed using the Bygum scale (2011). In our study, we only assessed the relationship between the patient's sex and history of certain symptoms (laryngeal AE, face and neck AE, abdominal attacks) but did not assess the effect of sex on the frequency of attacks. Previously, Bork et al. and Steiner et al. demonstrated that women are more susceptible to HAE attacks than men [16, 22]; however, a larger number of female patients and the tendency to asymptomatic disease in male patients indirectly suggest that the disease is milder in men.

Study Limitations

Considering that HAE is an orphan disease, no preliminary calculation of the sample size was conducted, and the study included all patients with HAE with C1-INH deficiency observed at the Institute of Immunology at the time of the study. Therefore, the sample of study participants cannot be considered sufficiently representative, which limits the ability to extrapolate the results and their interpretation to the general population of similar patients outside the study.

CONCLUSION

The study of a large sample of Russian patients assessed the structure of the population of patients with HAE and identified the demographic and clinical features of the HAE course in Russia.

Important data for practical healthcare have been obtained in the study. The existence of the problem of a long diagnostic delay of HAE has been clearly demonstrated. To solve the problem, it is necessary to increase awareness of this disease among physicians of all specialties, since diagnostic delay leads to high mortality among patients with HAE and unnecessary surgical interventions.

To increase the detection of HAE, it is also necessary to make a list of warning signs. As a result of the study, a number of HAE clinical features were identified, which can be used as the basis for such a list: family history, combination of recurrent AEs and abdominal attacks, and onset of AEs and/or abdominal attacks in early childhood.

We managed to demonstrate that every patient has a risk of developing life-threatening AE; therefore, all patients should be provided with on-demand therapy, regardless of whether they previously had such AEs. Moreover, the risk factors for life-threatening AE were identified: the patient's age (the older the patient, the higher the risk) and history of face and neck AE.

ADDITIONAL INFORMATION

Funding source. The study had no sponsorship.
Competing interests. The authors declare no competing interests.
Authors' contribution. I.A. Manto, E.A. Latysheva, T.V. Latysheva — study concept and design; I.A. Manto, E.A. Latysheva, Yu.A. Gornostaeva, A.M. Kostinova, E.N. Medunitsyna, T.N. Myasnikova, T.S. Romanova, N.Kh. Setdikova, E.A. Frolov, O.V. Shubina, T.V. Latysheva — data collection; I.A. Manto — data processing, statistical analysis; I.A. Manto, D.O. Timoshenko — writing the text; E.A. Latysheva, T.V. Latysheva — editing. 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 of the version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema — the 2017 revision and update. *Allergy*. 2018;73(8):1575–1596. doi: 10.1111/all.13384

2. Bork K, Aygören-Pürsün E, Bas M, et al. Guideline: hereditary angioedema due to C1 inhibitor deficiency: S1 Guideline of the German Society for Angioedema (Deutsche Gesellschaft für Angio deme, DGA), German Society for Internal Medicine (Deutsche Gesellschaft für Innere Medizin, DGIM), German Society for Otorhinolaryngology (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, DGHNO), German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI), German Society for Child and AdolescentMedicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin, DGKJ), German Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG), German Society for Pediatric Allergology and Environmental Medicine (Gesellschaft für P diatrische Allergologie und Umweltmedizin, GPA), German Association of ENT Surgeons (Deutscher Berufsverband der Hals-Nasen-Ohren- rzte, BVHNO), and the German HAE Patient Association (HAE-Vereinigung, Selbsthilfegruppe, HAESHG). *Allergo J Int*. 2019;28(1):16–29. doi: 10.1007/s40629-018-0088-5

3. Germenis AE, Speletas M. The genetics of hereditary angioedema the iceberg slowly emerges. *J Angioedema*. 2016;2(1):8–17.

4. Germenis AE, Speletas M. Genetics of hereditary angioedema revisited. *Clin Rev Allergy Immunol*. 2016;51(2):170–182. doi: 10.1007/s12016-016-8543-x

5. Obtułowicz K. Bradykinin-mediated angioedema. *Polish Arch Intern Med*. 2016;126(1-2):76–85. doi: 10.20452/pamw.3273

6. Bas M, Adams V, Suvorava T, et al. Nonallergic angioedema: role of bradykinin. *Allergy*. 2007;62(8):842–856. doi: 10.1111/j.1398-9995.2007.01427.x

7. Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. *Immunol Allergy Clin North Am*. 2017;37(3):513–525. doi: 10.1016/j.iac.2017.04.001

8. Caccia S, Suffritti C, Cicardi M. Pathophysiology of hereditary angioedema. *Pediatr Allergy Immunol Pulmonol*. 2014;27(4):159–163. doi: 10.1089/ped.2014.0425

9. Caballero T, Baeza ML, Cabañas R, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. *J Investig Allergol Clin Immunol*. 2011;21(6):422–441.

10. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69(5):602–616. doi: 10.1111/all.12380

11. Alonso ML, Valle SO, Tórtora RP, et al. Hereditary angioedema: a prospective study of a Brazilian single-center cohort. *Int J Dermatol*. 2020;59(3):341–344. doi: 10.1111/ijd.14676

12. Kesim B, Uyguner ZO, Gelincik A, et al. The turkish hereditary angioedema pilot study (TURHAPS): The first turkish series of hereditary angioedema. *Int Arch Allergy Immunol*. 2011;156(4):443–450. doi: 10.1159/000323915

13. Kargarsharif F, Mehranmehr N, Fard SZ, et al. Type I and type II hereditary angioedema: Clinical and laboratory findings in Iranian patients. *Arch Iran Med*. 2015;18(7):425–429.

14. Andrejević SS, Korošec P, Šilar M, et al. Hereditary angioedema due to C1 inhibitor deficiency in Serbia: two novel mutations and evidence of genotype-phenotype association. Mazoyer S, ed. *PLoS One*. 2015;10(11):e0142174. doi: 10.1371/journal.pone.0142174

15. Bouillet L, Launay D, Fain O, et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. *Ann Allergy, Asthma Immunol*. 2013;111(4):290–294. doi: 10.1016/j.anai.2013.07.012

16. Steiner UC, Weber-Chrysochoou C, Helbling A, et al. Hereditary angioedema due to C1 — inhibitor deficiency in Switzerland: clinical characteristics and therapeutic modalities within a cohort study. *Orphanet J Rare Dis*. 2016;11(1):43. doi: 10.1186/s13023-016-0423-1

17. Xu YY, Jiang Y, Zhi YX, et al. Clinical features of hereditary angioedema in chinese patients: New findings and differences from other populations. *Eur J Dermatology*. 2013;23(4):500–504. doi: 10.1684/ejd.2013.2105

18. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy, Asthma Immunol*. 2005;94(4):498–503. doi: 10.1016/S1081-1206(10)61121-0

19. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Ann Allergy, Asthma Immunol*. 2020;124(6):600–607. doi: 10.1016/j.anai.2020.02.018

20. Agostoni A, Aygorenpursun E, Binkley K, et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3):S51–S131. doi: 10.1016/j.jaci.2004.06.047

21. Bygum A, Fagerberg CR, Ponard D, et al. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency. *Allergy Eur J Allergy Clin Immunol*. 2011;66(1):76–84. doi: 10.1111/j.1398-9995.2010.02456

22. Bork K, Meng G, Staubach P, et al. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267–274. doi: 10.1016/j.amjmed.2005.09.064

23. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153–1158. doi: 10.1111/j.1365-2133.2009.09366.x

24. Craig T, Busse P, Gower RG, et al. Long-term prophylaxis therapy in patients with hereditary angioedema with C1 inhibitor deficiency. *Ann Allergy, Asthma Immunol*. 2018;121(6):673–679. doi: 10.1016/j.anai.2018.07.025

СПИСОК ЛИТЕРАТУРЫ

1. Maurer M., Magerl M., Ansotegui I., et al. The international WAO/EAACI guideline for the management of hereditary angioedema — the 2017 revision and update // World Allergy Organ J. 2018. Vol. 11, N 1. P. 1–20. doi: 10.1186/s40413-017-0180-1

2. Bork K., Aygören-Pürsün E., Bas M., et al. Guideline: hereditary angioedema due to C1 inhibitor deficiency: S1 Guideline of the German Society for Angioedema (Deutsche Gesellschaft für Angio deme, DGA), German Society for Internal Medicine (Deutsche Gesellschaft für Innere Medizin, DGIM), German Society for Otorhinolaryngology (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, DGHNO), German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI), German Society for Child and AdolescentMedicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin, DGKJ), German Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG), German Society for Pediatric Allergology and Environmental Medicine (Gesellschaft für P diatrische Allergologie und Umweltmedizin, GPA), German Association of ENT Surgeons (Deutscher Berufsverband der Hals-Nasen-Ohren- rzte, BVHNO), and the German HAE Patient Association (HAE-Vereinigung, Selbsthilfegruppe, HAESHG) // Allergo J Int. 2019. Vol. 28, N 1. P. 16–29. doi: 10.1007/s40629-018-0088-5

3. Germenis A.E., Speletas M. The genetics of hereditary angioedema: the iceberg slowly emerges // J Angioedema. 2016. Vol. 2, N 1. P. 8–17.

4. Germenis A.E., Speletas M. Genetics of hereditary angioedema revisited // Clin Rev Allergy Immunol. 2016. Vol. 51, N 2. P. 170–182. doi: 10.1007/s12016-016-8543-x

5. Obtułowicz K. Bradykinin-mediated angioedema // Polish Arch Intern Med. 2016. Vol. 126, N 1-2. P. 76–85. doi: 10.20452/pamw.3273

6. Bas M., Adams V., Suvorava T., et al. Nonallergic angioedema: role of bradykinin // Allergy. 2007. Vol. 62, N 8. P. 842–856. doi: 10.1111/j.1398-9995.2007.01427.x

7. Kaplan A.P., Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade // Immunol Allergy Clin North Am. 2017. Vol. 37, N 3. P. 513–525. doi: 10.1016/j.iac.2017.04.001

8. Caccia S., Suffritti C., Cicardi M. Pathophysiology of hereditary angioedema // Pediatr Allergy Immunol Pulmonol. 2014. Vol. 27, N 4. P. 159–163. doi: 10.1089/ped.2014.0425

9. Caballero T., Baeza M.L., Cabañas R., et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations // J Investig Allergol Clin Immunol. 2011. Vol. 21, N 6. P. 422–441.

10. Cicardi M., Aberer W., Banerji A., et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group // Allergy. 2014. Vol. 69, N 5. P. 602–616. doi: 10.1111/all.12380

11. Alonso M.L., Valle S.O., Tórtora R.P., et al. Hereditary angioedema: a prospective study of a Brazilian single-center cohort // Int J Dermatol. 2020. Vol. 59, N 3. P. 341–344. doi: 10.1111/ijd.14676

12. Kesim B., Uyguner Z.O., Gelincik A., et al. The turkish hereditary angioedema pilot study (TURHAPS): the first turkish series of hereditary angioedema // Int Arch Allergy Immunol. 2011. Vol. 156, N 4. P. 443–450. doi: 10.1159/000323915

13. Kargarsharif F., Mehranmehr N., Fard S.Z., et al. Type I and type II hereditary angioedema: clinical and laboratory findings in Iranian patients // Arch Iran Med. 2015. Vol. 18, N 7. P. 425–429.

14. Andrejević S.S., Korošec P., Šilar M., et al. Hereditary angioedema due to C1 inhibitor deficiency in Serbia: two novel mutations and evidence of genotype-phenotype association. Mazoyer S., ed. // PLoS One. 2015. Vol. 10, N 11. P. e0142174. doi: 10.1371/journal.pone.0142174

15. Bouillet L., Launay D., Fain O., et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients // Ann Allergy, Asthma Immunol. 2013. Vol. 111, N 4. P. 290–294. doi: 10.1016/j.anai.2013.07.012

16. Steiner U.C., Weber-Chrysochoou C., Helbling A., et. al. Hereditary angioedema due to C1 — inhibitor deficiency in Switzerland: clinical characteristics and therapeutic modalities within a cohort study // Orphanet J Rare Dis. 2016. Vol. 11, N 1. P. 43. doi: 10.1186/s13023-016-0423-1

17. Xu Y.Y., Jiang Y., Zhi Y.X., et al. Clinical features of hereditary angioedema in chinese patients: new findings and differences from other populations // Eur J Dermatology. 2013. Vol. 23, N 4. P. 500–504. doi: 10.1684/ejd.2013.2105

18. Roche O., Blanch A., Caballero T., et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain // Ann Allergy, Asthma Immunol. 2005. Vol. 94, N 4. P. 498–503. doi: 10.1016/S1081-1206(10)61121-0

19. Banerji A., Davis K.H., Brown T.M., et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States // Ann Allergy, Asthma Immunol. 2020. Vol. 124, N 6. P. 600–607. doi: 10.1016/j.anai.2020.02.018

20. Agostini A., Aygorenpursun E., Binkley K., et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond // J Allergy Clin Immunol. 2004. Vol. 114, N 3. P. 51–131. doi: 10.1016/j.jaci.2004.06.047

21. Bygum A., Fagerberg C.R., Ponard D., et al. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency // Allergy Eur J Allergy Clin Immunol. 2011. Vol. 66, N 1. P. 76–84. doi: 10.1111/j.1398-9995.2010.02456.x

22. Bork K., Meng G., Staubach P., et al. Hereditary angioedema: new findings concerning symptoms, affected organs, and course // Am J Med. 2006. Vol. 119, N 3. P. 267–274. doi: 10.1016/j.amjmed.2005.09.064

23. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey // Br J Dermatol. 2009. Vol. 161, N 5. P. 1153–1158. doi: 10.1111/j.1365-2133.2009.09366.x

24. Craig T., Busse P., Gower R.G., et al. Long-term prophylaxis therapy in patients with hereditary angioedema with C1 inhibitor deficiency // Ann Allergy, Asthma Immunol. 2018. Vol. 121, N 6. P. 673–679. doi: 10.1016/j.anai.2018.07.025

AUTHORS' INFO

*** Irina A. Manto**, MD, Research Associate;
address: 24, Kashirskoye shosse, Moscow, 115522, Russia;
ORCID: http://orcid.org/0000-0001-6432-394X;
eLibrary SPIN: 7944-5159; e-mail: irina.manto@yandex.ru

Elena A. Latysheva, MD, Dr. Sci. (Med.), Leading Research Associate;
ORCID: http://orcid.org/0000-0002-1606-205X;
eLibrary SPIN: 2063-7973; e-mail: ealat@mail.ru

Daria O. Timoshenko, MD;
ORCID: http://orcid.org/0000-0002-7585-1390;
eLibrary SPIN: 2714-0906; e-mail: d.o.timoshenko@gmail.com

Yulia A. Gornostaeva, MD, Cand. Sci. (Med.), Senior Research Associate;
eLibrary SPIN: 8191-5590; e-mail: ygornost@yandex.ru

Aristitsa M. Kostinova, MD;
ORCID: https://orcid.org/0000-0002-0584-2376;
eLibrary SPIN: 2922-5274; e-mail: aristica_kostino@mail.ru

Ekaterina N. Medunitsyna, MD, Cand. Sci. (Med.);
Senior Research Associate;
ORCID: https://orcid.org/0000-0002-7872-6261;
e-mail: medunitsyna.kate@yandex.ru

Tatyana N. Myasnikova, MD, Cand. Sci. (Med.);
Senior Research Associate;
ORCID: https://orcid.org/0000-0001-8491-195X;
SPIN-код: 4684-3112; e-mail: t_miasnikova@mail.ru

Tatyana S. Romanova, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-3350-3811;
eLibrary SPIN: 8027-8625; e-mail: ts_romanova@mail.ru

Nailya Kh. Setdikova, MD, Dr. Sci. (Med.), Leading Research Associate;
ORCID: https://orcid.org/0000-0003-2587-7928;
eLibrary SPIN: 6339-6945; e-mail: nh.setdikova@nrcii.ru

Evgeniy A. Frolov, MD;
ORCID: https://orcid.org/0000-0002-0800-5960;
eLibrary SPIN: 5963-4062; e-mail: frolovevgeny@rambler.ru

Olga V. Shubina, MD, Cand. Sci. (Med.);
eLibrary SPIN: 9010-4704; e-mail: shubina15@mail.ru

Tatiana V. Latysheva, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0003-1508-0640;
eLibrary SPIN: 8929-7644; e-mail: tvlat@mail.ru

ОБ АВТОРАХ

*** Манто Ирина Александровна**, н.с.;
адрес: Россия, 115522, Москва, Каширское шоссе, д. 24;
ORCID: http://orcid.org/0000-0001-6432-394X;
eLibrary SPIN: 7944-5159; e-mail: irina.manto@yandex.ru

Латышева Елена Александровна, д.м.н., в.н.с.;
ORCID: http://orcid.org/0000-0002-1606-205X;
eLibrary SPIN: 2063-7973; e-mail: ealat@mail.ru

Тимошенко Дарья Олеговна;
ORCID: http://orcid.org/0000-0002-7585-1390;
eLibrary SPIN: 2714-0906; e-mail: d.o.timoshenko@gmail.com

Горностаева Юлия Алексеевна, к.м.н., с.н.с.;
eLibrary SPIN: 8191-5590; e-mail: ygornost@yandex.ru

Костинова Аристица Михайловна;
ORCID: https://orcid.org/0000-0002-0584-2376;
eLibrary SPIN: 2922-5274; e-mail: aristica_kostino@mail.ru

Медуницына Екатерина Николаевна,
к.м.н., с.н.с.;
ORCID: https://orcid.org/0000-0002-7872-6261;
e-mail: medunitsyna.kate@yandex.ru

Мясникова Татьяна Николаевна,
к.м.н., с.н.с.;
ORCID: https://orcid.org/0000-0001-8491-195X;
SPIN-код: 4684-3112; e-mail: t_miasnikova@mail.ru

Романова Татьяна Сергеевна, к.м.н.;
ORCID: https://orcid.org/0000-0003-3350-3811;
eLibrary SPIN: 8027-8625; e-mail: ts_romanova@mail.ru

Сетдикова Наиля Харисовна, д.м.н., в.н.с.;
ORCID: https://orcid.org/0000-0003-2587-7928;
eLibrary SPIN: 6339-6945; e-mail: nh.setdikova@nrcii.ru

Фролов Евгений Александрович;
ORCID: https://orcid.org/0000-0002-0800-5960;
eLibrary SPIN: 5963-4062; e-mail: frolovevgeny@rambler.ru

Шубина Ольга Валерьевна, к.м.н.,
eLibrary SPIN: 9010-4704; e-mail: shubina15@mail.ru

Латышева Татьяна Васильевна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0003-1508-0640;
eLibrary SPIN: 8929-7644; e-mail: tvlat@mail.ru

* Corresponding author / Автор, ответственный за переписку