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Hereditary Angioedema with a mutation in the plasminogen gene: a retrospective study of a cohort of 14 patients from Russia

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ABSTRACT

BACKGROUND: In 2018, a new form of hereditary angioedema without C1-inhibitor deficiency — hereditary angioedema with a mutation in the plasminogen gene — was identified. The world scientific literature describes a small number of patients with this form of the disease and, therefore, new research is relevant.

AIMS: To identify the sociodemographic and clinical features of patients with hereditary angioedema with plasminogen gene mutation; to evaluate the treatment efficacy; to conduct a comparative analysis in a group of patients with hereditary angioedema type I/II.

MATERIAL AND METHODS: 14 patients (1 male and 13 females, mean age 51.64±13.55 years) with hereditary angioedema with c.988A>G mutation in the plasminogen gene (p.Lys330Glu; K330E) were enrolled in a retrospective study. The comparison group included 194 patients with hereditary angioedema type I/II (56 males and 138 females, mean age 37.03±16.23 years).

RESULTS: The average age at disease onset in patients with hereditary angioedema with a mutation in the plasminogen gene is 25.07±10.46 years, which is significantly higher than in patients with hereditary angioedema type I/II — 11.58±8.92 years (p <0.001). Peripheral angioedema was reported in 21.4% of patients with hereditary angioedema with a mutation in the plasminogen gene, abdominal attacks in 28.6%, which is less common than in patients with hereditary angioedema type I/II (peripheral edema 97.4%, p <0.001; abdominal attacks 86.6%, p <0.001). Face and neck angioedema was observed in all patients with hereditary angioedema with a mutation in the plasminogen gene (100%) and in 72.2% of patients in the group of hereditary angioedema type I/II (p=0.023). 85.7% of patients with hereditary angioedema with a mutation in the plasminogen gene had edema of the tongue. A decrease in the severity and duration of 28 out of 29 attacks by an average of 71.4% was reported by 4/5 of patients who used icatibant (Firazyr); 3/4 of patients reported a decrease in the frequency of attacks during treatment with tranexamic acid.

CONCLUSIONS: The disease's manifestation in adulthood, the predominance of face and tongue angioedema are common features of hereditary angioedema with a mutation in the plasminogen gene. The efficacy of tranexamic acid and icatibant was demonstrated in the observed cohort of patients.

Keywords: angioedema; hereditary angioedema; HAE; C1-inhibitor; plasminogen

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Наследственный ангиоотёк с мутацией в гене плазминогена: ретроспективное исследование когорты из 14 пациентов из России

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АННОТАЦИЯ

ОБОСНОВАНИЕ. В 2018 году выделена новая форма наследственного ангиоотёка без дефицита С1-ингибитора — наследственный ангиоотёк с мутацией в гене плазминогена. В мировой научной литературе описано небольшое число пациентов с этой формой заболевания, в связи с чем проведение новых исследований актуально.

ЦЕЛЬ — выявить характерные социодемографические и клинические особенности пациентов с наследственным ангиоотёком с мутацией в гене плазминогена; оценить эффективность терапии; провести сравнительный анализ с группой пациентов с наследственным ангиоотёком I/II типа.

МАТЕРИАЛ И МЕТОДЫ. В ретроспективное исследование включено 14 пациентов (1 мужчина и 13 женщин, средний возраст 51,64±13,55 года) с наследственным ангиоотёком с мутацией c.988A>G в гене плазминогена (p.Lys330Glu;K330E). Группу сравнения составили 194 пациента с наследственным ангиоотёком I/II типа (56 мужчин и 138 женщин, средний возраст 37,03±16,23 года).

РЕЗУЛЬТАТЫ. Средний возраст дебюта заболевания у пациентов с наследственным ангиоотёком с мутацией в гене плазминогена — 25,07±10,46 года, что значительно выше, чем у пациентов с наследственным ангиоотёком I/II типов — 11,58±8,92 года (p <0,001). Периферические отёки зафиксированы у 21,4% пациентов с наследственным ангиоотёком с мутацией в гене плазминогена, абдоминальные атаки — у 28,6%, что реже, чем у пациентов с наследственным ангиоотёком I/II типов (периферические отёки — 97,4%, p <0,001; абдоминальные атаки — 86,6%, p <0,001). Отёки области лица и шеи были у всех пациентов с наследственным ангиоотёком с мутацией в гене плазминогена (100%), в группе наследственного ангиоотёка I/II типов — у 72,2% (p=0,023). У 85,7% пациентов с наследственным ангиоотёком с мутацией в гене плазминогена были отёки языка. Уменьшение интенсивности и длительности 28 из 29 атак в среднем на 71,4% отметили 4/5 пациентов, применявших икатибант (Фиразир); 3/4 пациентов на фоне терапии транексамовой кислотой отметили снижение частоты атак.

ЗАКЛЮЧЕНИЕ. Дебют в зрелом возрасте, преобладание в клинической картине отёков лица и языка — характерные особенности течения наследственного ангиоотёка с мутацией в гене плазминогена. Продемонстрирована эффективность транексамовой кислоты и икатибанта у наблюдаемой когорты пациентов.

Ключевые слова: ангиоотёк; наследственный ангиоотёк; НАО; С1-ингибитор; плазминоген

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List of abbreviations

AE — angioedema
ACE inhibitor — angiotensin-converting enzyme inhibitor
HAE — hereditary angioedema
HAE-FXII — HAE due to a mutation in the coagulation factor XII gene
HAE-KNG1 — HAE due to a mutation in the kininogen 1 gene
HAE-PLG — HAE due to a mutation in the plasminogen gene
sGCS — systemic glucocorticosteroids
C1-INH — C1-inhibitor
SERPING1 (Serpin Family G Member 1) — serpin alpha-1
UNK-HAE — HAE due to an unknown mutation

Background

Hereditary angioedema (HAE) is an orphan, genetically determined, potentially life-threatening disease characterized by recurrent edema of the skin and mucous/submucosal membranes. The mediator bradykinin plays a key role in the development of angioedemas (AEs) in HAE. That is why these AEs are not sensitive to the standard therapy used to treat patients with AEs caused by mast cell mediators (systemic glucocorticosteroids; antihistamines; adrenaline), and require another, pathogenetically based therapy [1, 2].

HAE was first described in 1888 by the Canadian physician William Osler as a disease characterized by recurrent AEs in patients with a burdened family history. In 1963, the role of C1-esterase inhibitor deficiency in the pathogenesis of the disease was established. Several years later, HAE type II, associated with functional deficiency of the C1-inhibitor, was identified and in 1986, a mutation in the *SERPING1* gene, associated with C1-inhibitor deficiency and the development of HAE, was identified [3]. In 2000, a new HAE type, without deficiency of the C1-inhibitor, was first described and originally named HAE type III, over 20 years, mutations causally significant for the development of this type of HAE were identified in five genes (Table 1).

These discoveries were the reason for the revision of the HAE classification. Currently, the following HAEs are classified: with C1-inhibitor deficiency (HAE types I and II) and without C1-inhibitor deficiency (Fig. 1).

One of the most common genetic types of HAE without C1-inhibitor deficiency is HAE-PLG, discovered in 2018. The development of HAE-PLG is caused by the c.988A>G missense mutation in the *PLG* gene, as a result of which an amino acid substitution occurs in the structure of the plasminogen protein [7]. HAE-PLG, like other forms of HAE, has an autosomal dominant pattern of inheritance [11].

The prevalence of HAE-PLG is unknown. To date, several series of clinical cases have been described for a total of 146 patients from 33 families from European

Table 1. Causal mutations for hereditary angioedema without C1-inhibitor deficiency

Gene	Mutation	Discovery year	Discovered by
F12	c.983C>A c.983C>G	2006	Dewald, Bork [4]
F12	c.971_1018+24del72	2011	Bork et al. [5]
F12	c.892_902dup	2013	Kiss et al. [6]
PLG	c.988A>G	2018	Bork et al. [7]
ANGPT1	c.807G>T	2018	Bafunno et al. [8]
KNG1	c.1136T>A	2019	Bork et al. [9]
MYOF	c.651G>T	2020	Ariano et al. [10]

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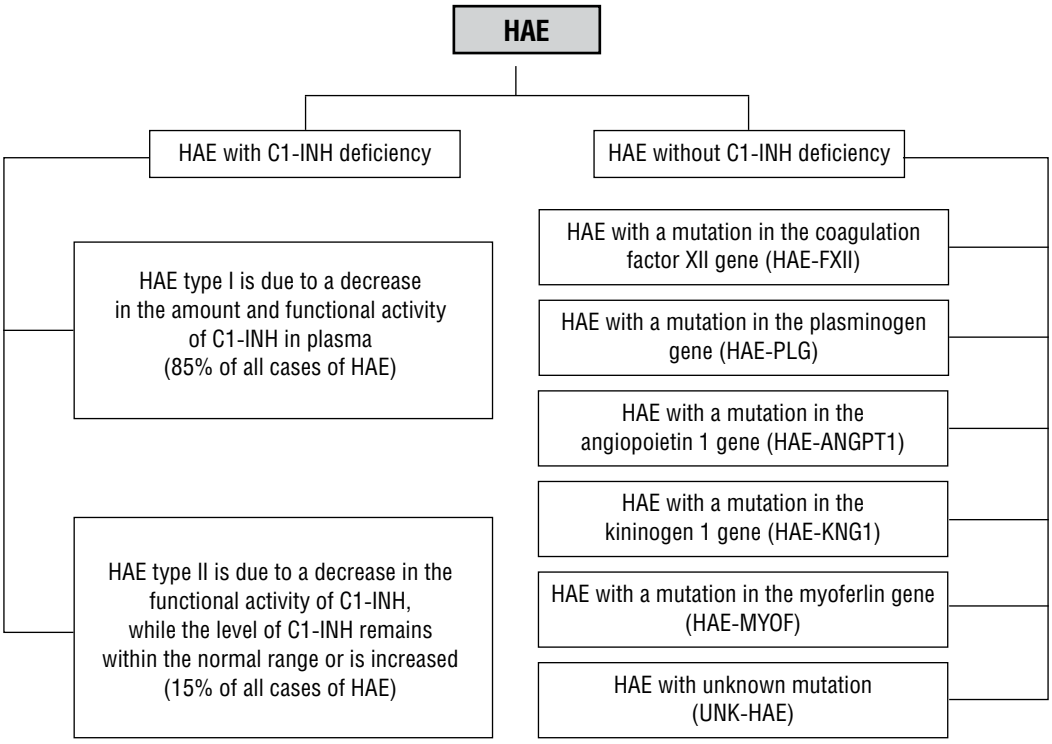

Fig. 1. Current classification of hereditary angioedema [1, 11].

Note. HAE — hereditary angioedema; C1-INH — C1-inhibitor.

countries (Germany [7, 12-14], France [15], Greece, Bulgaria, Spain [16]), Japan [17], and America [18]. The exact pathogenesis of HAE-PLG is also unknown: it is assumed that bradykinin is a key mediator, like for HAE with C1-inhibitor deficiency (due to the similarity of the course of the disease and approaches to treatment).[19]

Recurrent AEs of various localization, insensitive to the administration of antihistamines and systemic glucocorticosteroids (sGCS), is the main symptom for all forms of HAE. The features of HAE without C1-inhibitor deficiency, including HAE-PLG, have been insufficiently studied, but the available descriptions of clinical cases suggest that the features of the disease do not only exist for the group as a whole, but also for individual genetic types in particular [11].

HAE diagnosis established in time allows prescribing a proper therapy for the patient. However, even for a well-studied form of HAE with C1-inhibitor deficiency (HAE types I and II), the diagnosis delays years in various countries and is more than 10 in a large number of patients [20-23]. Diagnosing HAE-PLG is an even more challenging, which is due not only to the absence of objective biochemical signs, but also by the small number of descriptions of the features of the clinical course and management of such patients.

The purpose is to identify the sociodemographic and clinical features of patients with HAE-PLG; to evaluate the efficacy of drugs for on-demand treatment of AE and for long-term prophylaxis in this group of patients; to carry out a comparative analysis of clinical parameters in patients with HAE with C1-inhibitor deficiency (types I and II).

Materials and Methods

Study design

An observational retrospective sampling single-center study was conducted. The study included descriptive and analytical stages.

Eligibility criteria

The study enrolled 14 patients from 10 unrelated families with HAE-PLG. The study inclusion criteria were the presence of an identified missense mutation c.988A>G (p.Lys330Glu;K330E) in the *PLG* gene, as well as clinical symptoms of HAE (recurrent AEs of various localization and/or abdominal attacks) at the time of the study.

The comparison group included 194 patients diagnosed with HAE with C1-inhibitor deficiency from 124 unrelated families. The inclusion criteria were established diagnosis of HAE type I or II in accordance with the WAO/EAACI criteria [2, 24]; the presence of clinical symptoms of HAE (recurrent AEs of various localization and/or abdominal attacks) at the time of the study.

The exclusion criterion for both groups of patients was the absence of HAE symptoms (2 patients with a mutation in the plasminogen gene without clinical manifestations of the disease were not enrolled in the study).

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Conditions of the study conduct

The study was carried out at the clinical site of the Federal State Budgetary Institution National Research Center – Institute of Immunology Federal Medical-Biological Agency of Russia (hereinafter NRC Institute of Immunology FMBA of Russia). It is the result of many years of joint work of the Institute of Immunology, the Medical Genetic Research Center and immunologists of medical institutions from various regions of the Russian Federation on the diagnosis and treatment of hereditary and idiopathic AEs.

Study duration

The collection and processing of medical data was carried out from October to December 2020.

Description of the medical intervention

The sample of patients with HAE-PLG was formed from a cohort of 1,319 patients from 931 families referred with suspected HAE to the Medical Genetic Research Center named after N.P. Bochkov from the NRC Institute of Immunology FMBA of Russia and other medical institutions in Moscow, as well as other regions of the Russian Federation (St. Petersburg; Arkhangelsk, Saratov, Tambov, Tula regions; Republic of Bashkortostan) in the period from 2009 to 2020 for molecular genetic testing for the presence of mutations in all exons of the *SERPING1* gene, as well as pathogenic variants c.988A>G (p.Lys330Glu;K330E) of the PLG gene and c.983C>A (p.Thr328Lys) and c.983C>G (p.Thr328Arg) of the *F12* gene.

Patients with HAE types I and II, who were followed up in the clinic of the NRC Institute of Immunology FMBA of Russia were included in the comparison group. No medical intervention was carried out, as the study design provided retrospective data collection only, including on the efficacy of treatment.

Main study outcome

During the retrospective study, data important for practical healthcare were obtained on the clinical and sociodemographic characteristics of HAE-PLG (gender, average age, average age at disease onset, average age at diagnosis, delay in diagnosis, presence of a burdened family history, history of tracheostomy, surgical intervention, death of a relative due to AE). Disease manifestations were characterized by analyzing the incidence of clinical symptoms (peripheral edema, abdominal attacks, edema of the face and neck, edema of the tongue, edema of the larynx, marginal erythema); the incidence of the above symptoms as a starting symptom was analyzed. The efficacy of tranexamic acid as an option for long-term prophylaxis of AEs and icatibant as an option for AEs' on-demand treatment in patients with HAE-PLG was evaluated. A comparative analysis of samples of patients with HAE-PLG and HAE types I and II was performed.

Subgroup analysis

All enrolled patients were divided into two groups. The first group included 14 patients with HAE-PLG from 10 unrelated families, the second (comparison group) included 194 patients from 124 unrelated families with HAE types I and II. Comparative analysis between the two groups of patients was carried out for sociodemographic and clinical parameters, such as gender, average age, average age at disease onset, average age at diagnosis, delay in diagnosis, presence of a burdened family history, history of tracheostomy, surgery, death of a relative due to AE, the incidence of clinical symptoms (peripheral edema, abdominal attacks, edema of the face and neck, edema of the larynx). Comparative analysis of the incidence of edema of the tongue, edema of various localization as a starting symptom was not carried out due to the lack of this information in the medical records of patients from the comparison group. The efficacy of treatment in the two groups was not compared, as at the time of the study, data on the efficacy of treatment were only available for a small number of patients in the study group, and therefore the comparative analysis was not representative.

Outcome recording methods

Data on the features of the clinical manifestation of the disease, sociodemographic characteristics and the efficacy of treatment in the study sample of patients were obtained by analyzing the medical records of patients and the database of NRC Institute of Immunology FMBA of Russia . In the event that patient data were collected more than 2 years ago or were not collected in full, the study doctor updated the information in accordance with the questionnaire developed by us (Appendix). The data obtained were structured into a MS Excel table (USA).

Ethical review

The study was approved by the Local Ethics Committee of the Federal State Budgetary Institution National Research Center – Institute of Immunology Federal Medical-Biological Agency of Russia, Minutes No. 9 dated September 17, 2020.

Statistical analysis

During the study, descriptive and comparative statistical analysis of data was carried out using statistical processing software, including IBM SPSS Statistics (USA), MS Excel (USA). To carry out descriptive statistical analysis, parameters such as the arithmetical mean and standard deviation of the sample were used. Analysis of quantitative data was performed using the Mann-Whitney U-test, and analysis of qualitative data using the Pearson chi-square (χ^2) test. The difference was considered statistically significant at $p < 0.05$.

Since HAE-PLG is currently an orphan disease with unknown prevalence, it was not possible to perform a preliminary sample calculation. The sample calculation for hereditary angioedema type I/II was not performed for the same reasons.

Results

Study subjects (participants)

In the study sample of patients with HAE-PLG (n=14), there were 13 women (92.9%), 1 men (7.1%); the average age was 51.64±13.55 (29-71) years. The average age at disease onset for patients with HAE-PLG was 25.07±10.46 (12-45) years, the average age at diagnosis was 51.14±14.04 years, and delay in diagnosis 25.36±16.80 years.

Key study results

All patients (100%) had a history of at least one episode of edema of the face and neck, 12 patients (85.7%) had edema of the tongue, and 11 patients (78.6%) had edema of the larynx. In the history of 2 (14.3%) patients, only AEs of the face, neck and tongue were present. Abdominal attacks were in the history of 4 (28.6%) patients, peripheral edema in 3 (21.4%) patients, and marginal erythema only in 1 (7.1%) patient.

Edema of the face and neck was the starting syndrome for 11/14 (78.6%) of the described patients. In one (7.1%) case each, the disease onset was associated with an abdominal attack and edema of the larynx, respectively. An episode of simultaneous abdominal attack and peripheral edema was also the starting syndrome in 1 (7.1%) patient.

All patients with HAE-PLG had a positive family history (100%); death of a relative was in the history of 6 (42.9%) patients from 4 (40%) families. 2 (14.3%) patients underwent surgical intervention due to an abdominal attack, 1 (7.1%) patient underwent tracheostomy due to inefficacy of therapy for edema of the tongue.

We evaluated the treatment efficacy prescribed in the HAE-PLG group: 6 (42.9%) patients from the study cohort did not need to take drugs for long-term prophylaxis due to the low frequency of AE (1-6 episodes per year); 8 (57.1%) were assessed by doctors as patients who needed long-term prophylaxis (the frequency of AE is higher than once per month), but currently only four of them receive treatment — tranexamic acid (TA) at a dose of 1 to 3 g/day for 6-24 months. In three (75%) of 4 patients a decrease in the frequency of AE during treatment was indicated, 1 (25%) patient did not notice any changes. On average, the frequency of AE in patients taking TA decreased by 72.6%: the average frequency of attacks before the use of TA was 26.5 per year, and 7.25 per year during the use of TA.

Icatibant for on-demand treatment of AE was used by 5/14 (35.7%) patients, the drug was administered for acute therapy of 29 attacks, while 4/5 (80%) patients noted a decrease in the duration of AE (when used in 28 attacks out of 29), 1 (20%) patient reported that the drug was ineffective in relieving one attack. On average, the duration of attacks in patients using this drug was reduced by 71.4%. The average duration of attacks was 42 hours without the use of icatibant and 12 hours with the use of icatibant. None of the patients described by us used a C1-inhibitor or fresh frozen plasma for on demand therapy of AE.

In addition to the description of the group of patients with HAE-PLG, we also carried out a comparative analysis of two groups of patients: with HAE with C1-inhibitor deficiency (n=194) and HAE-PLG (Table 2, Fig. 2).

As it's shown in Table 2, patients with HAE-PLG are characterized by a later onset of the disease (p <0.001) ad elder age of diagnosis (p <0.001). Despite the fact that the average delay in diagnosing HAE types I and II was 17.54±13.29, and HAE-PLG 25.36±16.80 years, the difference was statistically insignificant (p=0.089). Every fourth patient with HAE types I and II had no family history, while patients with HAE-PLG had a family history if the disease in all cases (p=0.023). In the HAE-PLG group, cases of death of a relative from AE were also significantly more frequent.

The comparative analysis of AEs' localizations in patients with HAE with C1-inhibitor deficiency and with

Table 2. Comparative analysis of clinical and sociodemographic characteristics of patients with hereditary angioedema with C1-inhibitor deficiency and HAE-PLG

Parameters	HAE with C1-inhibitor deficiency, n=194	HAE-PLG, n=14	p
Average age, years	37.03±16.23	51.64±13.55	0.02
Gender female/male (%)	138/56 (71.1/28.9)	13/1 (92.9/7.1)	0.118
Average age at onset, years	11.58±8.92	25.07±10.46	< 0.001
Average age at diagnosis, years	29.20±15.11	51.14±14.04	< 0.001
Delay in diagnosis, years	17.54±13.29	25.36±16.80	0.089
Family history, number of patients (%)	141 (72.7)	14 (100)	0.023
Surgical intervention, number of patients (%)	39 (20.1)	2 (14.3)	1
Tracheostomy or intubation, number of patients (%)	9 (4.6)	1 (7.1)	0.5
Death of a relative due to angioedema, number of patients (%)	42 (21.7)	6 (42.9)	0.023

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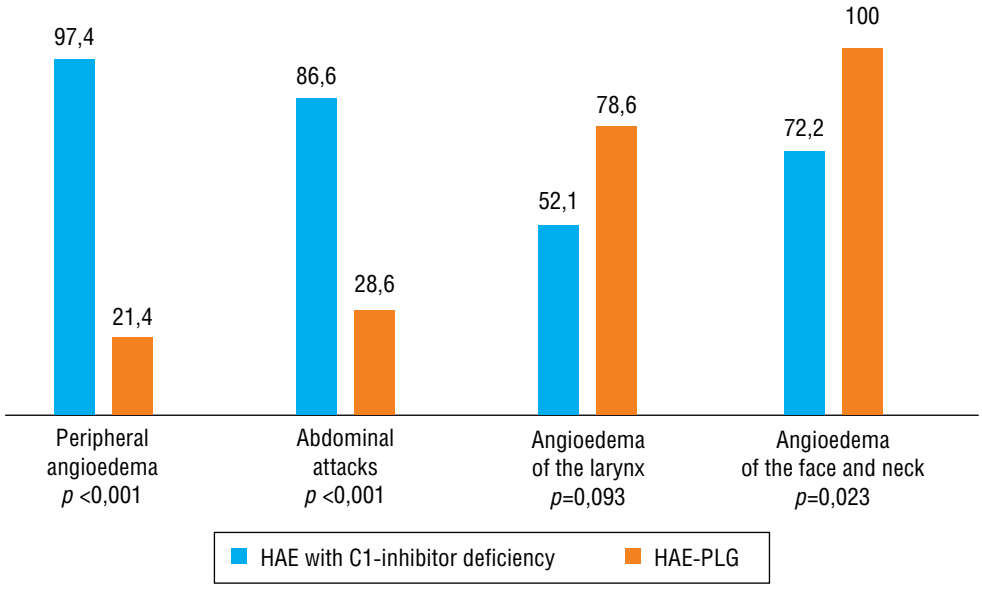

Fig. 2. Comparative analysis of angioedema localization in patients with hereditary angioedema with C1-inhibitor deficiency (n=194) and HAE-PLG (n=14),%.

HAE-PLG (see Fig. 2) demonstrated that peripheral AEs and abdominal attacks were much more common in the history of patients with HAE with C1-inhibitor deficiency (p <0.001 for both indicators). AEs of the face and neck are more typical for patients with HAE-PLG (p=0.023). Despite that larynx AE is more typical for HAE-PLG (see Fig. 2), this difference was statistically insignificant (p=0.093).

Additional study findings

At the time of diagnosis, two (14.3%) of 14 patients with HAE-PLG were taking antihypertensive therapy with drugs that can enhance the manifestations of HAE: one patient received an angiotensin II receptor antagonist, and another one an angiotensin-converting enzyme (ACE inhibitor) inhibitor. On the background of this treatment, almost continuously recurrent AEs of various localization were observed (peripheral AEs; AEs of the tongue, face; abdominal attacks). After these drugs were replaced with another, both patients noted the decrease of AEs' frequency; however, complete remission of the disease was not achieved (the incidence of AE persisted up to once per month in the first patient and up to 3 times per month in the second patient). In addition, another patient noted the relationship between the appearance of AE of the face after using an ACE inhibitor, which was used to lower blood pressure on demand. One patient had a history of using an estrogen-containing drug (as part of a combined oral contraceptive), she noted no increase in the frequency and/or severity of AEs on the background of this therapy.

Adverse events

Adverse events were not recorded during the study, as the study design provided retrospective data analysis only.

Discussion

Summary of the main study result

As a result of our study, we found that patients with HAE-PLG are characterized by a later age of disease onset than patients with HAE with C1-inhibitor deficiency. In the clinical picture of the disease in patients with HAE-PLG, AEs of the face and tongue predominate. Abdominal attacks and peripheral AE are less common than in patients with HAE types I and II. Tranexamic acid and icatibant are effective in the treatment of patients with HAE-PLG.

Discussion of the main study result

Since there is currently very few data on rare forms of HAE, the description of these groups of patients represents the scientific interest. We found that in the studied cohort of patients with HAE-PLG, female patients predominated (at a ratio of 13:1), this is consistent with the data of previous studies of this type of HAE [7, 12, 15, 17]. Such a pronounced prevalence of female patients, despite the autosomal dominant inheritance, is also described for HAE-FXII and is probably explained by the lower penetrance in men than in women [25]. For HAE-FXII, the presence of gender-dependent penetrance is explained by the characteristic triggering activating effect of estrogens in the event of angioedema [26, 27]. However, in patients with HAE-PLG, in contrast to other types of HAE without C1-inhibitor deficiency, the effect of estrogen seems less obvious. One patient from the described cohort did not note an increase in the frequency of AEs while taking an estrogen-containing contraceptive. None of the described patients showed a relationship between the development of AE and puberty, pregnancy, or lactation. According to data from foreign

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colleagues, estrogen-containing drugs were a trigger for the development of AE only in a small number of patients with HAE-PLG who took them — in 22.6%. In other cases (77.4% of patients) taking such drugs did not affect the course of the disease in any way [7]. At the same time, in the majority of patients with HAE with C1-inhibitor deficiency, taking estrogen-containing drugs significantly worsened the course of the disease (in 60% of patients in a study by K. Bork et al. [28], in 67.4% in a study by C. Saule et al. [29], and 80% in a study by L. Bouillet et al. [30]). For most patients with HAE-FXII, estrogen-containing drugs are also considered a key trigger factor. Thus, the study by K. Bork et al. [31] showed that 90.7% of patients with HAE with a mutation in the *F12* gene who took oral contraceptives containing estrogen had recurrent AEs. In 78.6% of patients who stopped taking drugs, AE no longer recurred [31]. This difference is one of the distinguishing features of the HAE-PLG subtype, and therefore the absence of AE during the use of estrogen-containing oral contraceptives should not prevent the doctor from the diagnostic search for HAE in a patient with recurrent AEs. However, given the small sample of patients and the small number of observations to make definitive conclusions, the use of estrogen-containing drugs should be avoided in patients with HAE-PLG.

It is known that ACE inhibitors and angiotensin II receptor antagonists are specific triggers for HAE with C1-inhibitor deficiency and HAE-FXII [2, 25]. Using these groups of drugs increases the risk of developing AEs, including of life-threatening localization. In 3 patients of the studied cohort, the use of drugs from the groups of ACE inhibitors and angiotensin II receptor antagonists also had a significant effect on the course of HAE. The role of these drugs in the development of AEs in patients with HAE-PLG has also been previously described in foreign literature [7, 12, 13, 15–17]. These data should be taken into account when prescribing antihypertensive treatment to patients with HAE-PLG, as well as to patients with other forms of HAE. Patients who have manifestated with AEs while taking drugs from these groups need to be examined to exclude HAE, including that without C1-inhibitor deficiency.

The most common localization of AE in our sample of patients with HAE-PLG was the face and neck (100% of patients), tongue (85.7%), and larynx (78.6%). Despite the fact that abdominal attacks were in the history of a small number of patients (28.6%), they could cause unjustified surgical intervention in 14.3% of patients, as in the case of HAE with C1-inhibitor deficiency. Thus abdominal attacks in patients with HAE-PLG are also very painful and can clinically resemble acute abdominal syndrome. The obtained data on AE localization are comparable with the data of foreign literature, which also showed the predominance of angioedema of the face, tongue and larynx over abdominal attacks and peripheral agioedema in the clinical presentation of HAE-PLG [7, 15]. In the study by K. Bork et al. [7], 18.33% of patients only had a history of tongue angioedema. The patient described by D. Bodian et al. [18], also suffered from angioedema of this localization only. In our cohort, there were no patients with isolated tongue AEs; however, 14.3% of them had AEs of the face, neck and tongue only.

AE in HAE-PLG, as well as in HAE with C1-inhibitor deficiency can be lethal. In 42.9% of patients in the described cohort the history was burdened with the death of a relative due to AE; comparable data were described in foreign studies [7, 12, 15, 17]. One (7.1%) patient from our study cohort underwent tracheostomy due to AE of the tongue. Data on the frequency of this manipulation among patients with HAE-PLG are not presented in the foreign literature; however, the study by K. Bork et al. [7] described two deaths due to asphyxiation caused by edema of the tongue.

The presence of the disease family history was described for all our patients with HAE-PLG. Since there is no specific biochemical sign for the HAE-PLG subtype, the diagnosis can only be suspected in the presence of a burdened family history. Isolated cases, could be more likely missed by doctors than in HAE with C1-inhibitor deficiency, when there is an additional biochemical criterion [26].

Our patients with HAE-PLG are characterized by a late disease onset — not earlier than the second decade of life, which is also consistent with the data of foreign colleagues [7, 12, 15, 17]. In the study group, face AE (78.6%) was a the most often starting symptom. Taking into account that this clinical parameter was not evaluated in previously described groups of patients with HAE-PLG, our data are of great importance in the phenotypic characteristics of this subtype of HAE.

The diagnostic delay in patients with HAE-PLG averaged 25.36±16.80 years. The time of the delay in diagnosis was previously considered only in one study conducted in a cohort of patients in France, its median was 24.00 years, which was consistent with our findings [15]. The significant delay in diagnosis in patients with HAE-PLG, even if they have a burdened family history, is largely due to the fact that this subtype of HAE was only isolated in 2018, when a causal mutation in the plasminogen gene was described.

There are three main components of HAE therapy: on demand therapy, short-term and long-term prophylaxis [1, 2]. To date, there is very few evidence on the management of patients with HAE-PLG. The small number of patients with HAE-PLG impedes the conduct of large randomized clinical trials; nevertheless, the risk of potentially fatal AEs creates an urgent need to search for pathogenetic therapy with the formation of an evidence base. Currently the pathogenesis of HAE-PLG is not fully understood; however, it is believed that bradykinin is the key mediator (like for HAE types I and II), and, therefore, it is of particular interest to study the effect of drugs that proved their efficacy in HAE with C1-deficiency-inhibitor.

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Two drugs are available in Russia for on demand treatment of AEs in patients with HAE — icatibant and a C1-inhibitor. Icatibant is a synthetic decapeptide, that is a competitive and selective type 2 bradykinin receptors (B2 receptor) antagonist. The drug is produced as a pre-filled syringe containing 3 mL (30 mg) solution. Icatibant is manufactured for subcutaneous injection which makes self-administration of the drug by patients easily feasible, minimizing the time spent on providing emergency care[1]. The drug has shown high efficacy and safety when used in patients with HAE types I and II, not only in large-scale multicenter studies, but also in many years of clinical practice, and is recommended for use in Russia and worldwide [1, 2].

Patients in the study group used the originator drug icatibant (Firazyr)[1], since at the time of the study, generics of the drug were not authorized. The drug was used to treat 29 attacks in 5 patients; in 28 cases, there was a decrease in the duration of AEs (1 patient noted no effect of treatment for 1 attack). In the foreign literature, the results of only one retrospective observational study conducted by K. Bork et al. [14], with an analysis of the treatment efficacy in 111 patients with HAE-PLG, have been published. The use of icatibant was shown to be effective in 11 of 13 patients. A decrease in the duration of AE symptoms by 88% with the treatment of the drug was noted when evaluating 201 attacks treated with icatibant and 149 previous non-treated attacks in 13 patients. The average duration of AE was 44.7±28.6 hours without treatment, and 4.3±2.6 hours with the use of the drug. Considering the positive experience of using icatibant in patients with HAE-PLG by foreign colleagues [14], as well as a pronounced effect of using it in 80% of patients in our cohort, prescribing the drug as a drug for on demand therapy of AE is preferable.

None of the described patients with HAE-PLG used C1-inhibitor for on demand therapy, but there are data in the foreign literature on its efficacy; however, the efficacy rate and the rate of AE resolution turned out to be lower than with the use of icatibant. In the study by K. Bork et al. [14], the C1-inhibitor was shown to be effective in 7 of 12 patients. The duration of 74 AEs in 12 patients was compared with the duration of 129 AEs in the same patients without treatment and was 44% less (the average duration of edemas without treatment was 48.2±32.5 hours and with the use of a C1-inhibitor 31.5±18.6 hours) [14]. To date, data are also available that confirm the efficacy of icatibant and a C1- inhibitor for the general population of patients with HAE without C1-inhibitor deficiency [32, 33].

Despite the fact that the effect of sGCS is uncharacteristic for AEs induced by bradykinin, patients with HAE-PLG can note a positive effect from this type of therapy. Thus, in the study by K. Bork et al. [14], sGCS showed high efficacy in 8 out of 35 patients when used during 61 out of 268 attacks, low efficacy in 7 out of 36 patients during 82/268 attacks, and were ineffective in 26 out of 36 patients when used during 125/268 attacks. Antihistamines were ineffective in 5 out of 5 patients during 37/37 attacks. sGCS and antihistamines used in combination showed high efficacy in 4 out of 23 patients during 13/309 attacks, low efficacy in 7 out of 23 patients during 150/309 attacks, and were ineffective in 17 out of 23 patients during 146/309 attacks. Fresh frozen plasma was used to relieve AE in two patients and in both cases did not affect the progression of AEs [14]. These data should be taken into account when carrying out differential diagnostics of AE.

Among described patients with HAE-РДП receiving TA as a drug for long-term prophylaxis, 75% noted a decrease in the frequency of AEs by an average of 72.6%. In the majority of patients taking TA described by foreign authors, the frequency of AEs also decreased, and in some patients the course of the disease became asymptomatic [7, 14, 17, 34]. The study by K. Bork et al. [14] also showed a decrease in the frequency of attacks in patients receiving TA (in 3 patients, the frequency of attacks decreased by an average of 93.9%). Taking into account our data, as well as the data of foreign colleagues, TA is effective in HAE-PLG, as well as in other forms of HAW without C1-inhibitor deficiency.

Currently we do not have our own experience with danazol as a long-term prophylaxis for HAE-PLG. The experience of foreign colleagues is still very limited, but given the available data (in 3 patients in the study by K. Bork et al. [14], receiving danazol, the frequency of attacks decreased by an average of 83.3%), the use of danazol can also be effective. We also do not have our own experience of prescribing progestins to patients with HAE-PLG. According to the data obtained in the study by K. Bork et al. [14], in the group of patients taking progestins for long-term prophylaxis, the frequency of attacks decreased by an average of 46%, while progestins were very effective in those patients only (in 2 out of 6) who had previously stopped taking estrogen-containing drugs. Partial efficacy of progestins was observed in 1 patient out of 6; in 3 out of 6 patients, progestins did not affect the frequency of AEs [14]. At the same time, a number of studies have shown high efficacy of progestins in patients with HAE-FXII [31], as well as in the general population of patients with HAE without C1-inhibitor deficiency [35]. Based on the data presented, it can be assumed that progestins are not as effective in HAE-PLG as in HAE-FXII. However, further research on this issue is required. The choice of drugs for short-term prophylaxis in patients with HAE-PLG remains difficult due to the lack of research on this issue.

Despite the fact that, in general, the clinical picture of HAE-PLG and HAE with C1-inhibitor deficiency is

[1] Patient Information Leaflet for Firazyr®. Access mode: https://apteka.hk/instrukciya/firazyr.pdf. Retrieval date: February 15, 2021

very similar (the main symptom is recurrent AE), when conducting a comparative analysis of these cohorts of patients, we were able to identify a number of significant differences. First, the mean age at disease onset is significantly higher in the HAE-PLG cohort. HAE with C1-inhibitor deficiency is characterized by an onset in the 1st and 2nd, and HAE-PLG in the 2nd, 3rd, and 4th decades of life. The data obtained indicate that such patients can be seen by physicians at any age, despite the widespread misconception that patients with hereditary diseases are mainly children. Thus, it is important that physicians of all specialties are aware of this form of HAE, especially taking into account that older patients are more likely to require antihypertensive therapy, and the administration of ACE inhibitors and angiotensin II receptor blockers to patients with HAE can worsen the course of the disease and lead to the development of life-threatening attacks. Second, there are significant differences in the typical localization of AEs. For HAE-PLG, AEs of the face and tongue come to the fore in the clinical picture, while only a small number of patients with HAE-PLG suffer from peripheral AEs and abdominal attacks, which are the main symptoms in HAE with C1-inhibitor deficiency. Thus, the clinical picture of HAE-PLG is more similar to the AEs induced by taking ACE inhibitors [36]. The features of localization of AE in HAE-PLG revealed by us indicate that it is necessary to carry out differential diagnostics with HAE even in patients with isolated AE of the face and tongue.

Comparative analysis of the clinical characteristics of patients with HAE-PLG and HAE-FXII in the study by K. Bork et al. [7] showed that different disease genotypes belonging to the same type (HAE without C1-inhibitor deficiency) have their own phenotypic features. Our data are also convincing that each type and subtype of HAE, with its characteristic clinical features and characteristics of the pharmacological response, require individual management approaches.

Study limitations

This study had limitations due to the small number of patients with HAE-PLG in the general patient population, and therefore the sample size to achieve the required statistical power of the results was not calculated. Thus, the sample of participants obtained during the study cannot be considered sufficiently representative, which does not allow extrapolating the obtained results (and their interpretation) to the general population of similar patients beyond the study.

Conclusion

On the one hand, HAE with C1-inhibitor deficiency and HAE-PLG are similar: in the population of patients with both forms, women predominate; both forms of the disease have an autosomal dominant inheritance pattern; are characterized by recurrent AE, which can lead to death; icatibant is effective as a drug for the on-demand therapy of AE in patients with both forms. On the other hand, this study and the results of previous studies revealed significant differences between HAE-PLG and HAE with C1-inhibitor deficiency: HAE-PLG is characterized by a late onset; the disease, as a rule, is manifested with AE of the face; in the clinical picture of the disease, AE of the face and tongue prevails, and in some patients this is the only symptom of the disease; estrogen-containing drugs are not always trigger factors in the development of AE. Knowledge of these features will allow the practicing physician not to miss a patient with HAE-PLG at the visit, timely establish the correct diagnosis and prescribe adequate treatment.

Additional info

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Appendix

Individual questionnaire

FULL NAME _____
Date of birth and age _____
Gender _____
Type of hereditary angioedema (HAE) _____
Deaths in the family from manifestations of HAE _____
History of tracheostomy _____
History of surgical intervention _____
Age at onset of first symptoms _____
Age at diagnosis _____
History of peripheral edema _____
History of abdominal attacks _____
History of edema of the tongue _____
History of edema of the face and neck _____
History of edema of the tongue _____
History of marginal erythema _____
Previous drugs for long-term prophylaxis _____
Frequency of attacks before taking drugs for long-term prophylaxis _____
Frequency of attacks during taking drugs for long-term prophylaxis _____
Previous drugs to relieve edema _____
Duration of attacks without the use of drugs to relieve edema _____
Duration of attacks with the use of drugs to relieve edema _____
Previous drugs from the groups of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, estrogen-containing drugs _____