Modern views on the diagnosis and treatment of hereditary angioedema: The importance of timely diagnosis and further management of the patient

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The review focused on managing patients with hereditary angioedema by administering C1-INH concentrate therapy. Hereditary angioedema is an orphan disorder characterized by recurrent episodes of angioedema, usually localized to the skin/subcutaneous tissue or mucous membranes of the upper respiratory tract and gastrointestinal tract and does not respond to usual treatment with antihistamines, corticosteroids, or adrenaline. Suspicion of HAE I or HAE II should be the basis for requesting laboratory tests to confirm the diagnosis. Determination of the function of C1-INH, C1-INH protein and C4 in serum/plasma is used to diagnose HAE I or HAE II. Own clinical case of the patients with HAE was proposed. Typical complex therapy includes a number of measures to avoid triggers of exacerbations and the development of a clear drug treatment plan with the patient (treatment of the acute condition, short-term (pre-procedural) and long-term prophylaxis). The importance of a multidisciplinary approach in the management of the patients with HAE is an important step towards timely verification of this rare/orphan disease.

Key words: Hereditary angioedema, diagnosis, C1-INH concentrate therapy.
Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterized by recurrent episodes of angioedema (AE), usually localized to the skin and subcutaneous tissue or mucous membranes of the upper respiratory tract (URT) and gastrointestinal tract (GI). Angioedema is not associated with swelling or itching and does not respond to usual treatment with antihistamines, corticosteroids, or adrenaline [1]. The prevalence of HAE in the population ranges from 1:10 000 to 1:50 000 [2], i.e. in Ukraine the number of such patients per 35 million population should be approximately 960 people. At the same time, the real number of diagnoses of HAE today is 105 people. A small proportion of patients diagnosed with HAE in our country are the result of a lack of awareness among doctors about this pathology. Delay in diagnosis is accompanied by the problem of untimely treatment seizures and can lead to the development of dangerous complications, which leads to a significant decrease in the quality of life of patients. Subcutaneous attacks of HAE, causing deformity, dysfunction, and disfigurement of the limbs, trunk, or face, often cause severe psychosocial distress. HAE attacks can manifest by submucosal changes in either the upper respiratory tract or the intestinal tract. Episodes of laryngeal edema pose a severe threat to life, potentially leading to suffocation, and in some instances, necessitating intubation or tracheostomy for resolution, actions that could have been prevented with appropriate treatment. Intestinal manifestations of HAE can simulate symptoms resembling acute surgical pathology potentially leading to surgical interventions like appendectomy [3]. These symptoms may develop spontaneously or in response to different triggers such as trauma, psychological stress, or infections. HAE results from an overproduction of the vasoactive peptide bradykinin due to inadequate levels of C1-inhibitor (C1-INH), which fail to inhibit plasma kallikrein enzymes and activated factor XII effectively. The location, frequency, and severity of HAE attacks exhibit significant variability within and between individuals [4].

Different forms of HAE are recognized and verified by genetic investigations [5]:

HAE due to C1-INH protein deficiency (HAE type 1, HAE I). This type is characterized by low levels of both antigenic and functional C1-INH protein. C1-INH (C1 esterase inhibitor) is a protein that helps regulate inflammation and prevents excessive activation of the complement system, a part of the immune system. When there’s a deficiency of functional C1-INH, it can lead to uncontrolled activation of the complement system, resulting in angioedema.

HAE due to C1-INH protein dysfunction (HAE type 2, HAE II). Unlike HAE type 1, in this type, the antigenic level of C1-INH protein may be normal or even elevated, but its function is impaired. This means that although there might be enough C1-INH protein present in the bloodstream, it doesn't work effectively in regulating inflammation and preventing angioedema.

HAE with mutation of the myoferlin gene (HAE-MIOF). Myoferlin is a protein involved in membrane repair and vesicle trafficking. Mutations in the myoferlin gene can lead to dysfunctional myoferlin protein, which may contribute to the development of angioedema in this subtype of HAE.

HAE with heparan sulfate 3-O-sulfo-transferase gene mutation (HAE-HS3ST6). Heparan sulfate 3-O-sulfotransferase is an enzyme involved in modifying heparan sulfate, a type of glycosaminoglycan found on cell surfaces and in the extracellular matrix. Mutations in the gene encoding this enzyme can affect the structure or function of heparan sulfate, potentially leading to angioedema in affected individuals.

The HAE is a disease that significantly affects life expectancy, its quality not only for patients, but also for their family members/caregivers. Early diagnosis, initiation of treatment and timely prevention contribute to the prevention of disability and premature death of patients [6].

C1-INH functions as a serine protease inhibitor (SERPIN), primarily inhibiting various complement proteases (C1r, C1s, lectin-binding serine protease MASP-1 and MASP-2), and contact system proteases (plasma kallikrein and coagulating FXIIa), alongside exerting a minor inhibitory effect on plasmin fibrinolytic protease. Bradykinin, a low molecular weight nanoprotein, serves as the primary mediator of edema in HAE I or HAE II, generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Most cases of Angioedema are attributed to mutations in the SERPING1 gene, encoding C1-esterase inhibitor (C1-INH). Two types of HAE associated with dysfunctional plasma C1-INH are recognized: most patients (85%) with HAE type I have low levels of complement C4, C1-INH and also C1-INH functional activity. In the case of HAE type II (15%) are typical low complement C4 level, low or normal C1-INH level and C1-INH functional activity [7, 8].

Acquired angioedema can occur as a result of C1-INH deficiency of secondary genesis, which is due to the formation of autoantibodies to it (in autoimmune diseases, hemoblastosis, parasitic invasions).
It's important to note that angioedema episodes in HAE I or HAE II can vary in severity and frequency among affected individuals. Some may experience relatively mild episodes, while others may have more severe and frequent attacks. The characteristic feature of HAE I or HAE II is the recurrent nature of these episodes, often without an obvious trigger. Given the potential severity of laryngeal edema in HAE, it's crucial for healthcare providers to have a high index of suspicion for HAE I or HAE II in patients presenting with recurrent unexplained swelling, particularly if it involves the gastrointestinal tract or the airway. Although 25% of patients may not have it [4,9]. It is also important to pay attention to patients whose first episodes of symptoms appeared in childhood/adolescence; recurrent abdominal pain is present; episode of edema of non-allergic origin; no response to antihistamines, corticosteroids, or epinephrine; presence of prodromal signs or symptoms prior to edema and/or absence of urticaria. Suspicion of HAE I or HAE II should be the basis for requesting laboratory tests to confirm the diagnosis. Determination of the function of C1-INH, C1-INH protein and C4 in serum/plasma is used to diagnose HAE I or HAE II.

Differential diagnosis of HAE I or HAE II includes other forms of HAE, for example, acquired angioedema due to C1-INH deficiency, angioedema induced by ACE inhibitors, angioedema mediated by mast cells (in patients with chronic spontaneous urticaria without papules, allergic angioedema), as well as idiopathic angioedema [2, 4].

Treatment is comprehensive and includes a number of measures to avoid triggers of exacerbations (use of estrogens, oral contraceptives, plasminogen activators, emotional stress) and the development of a clear drug treatment plan with the patient. Drug therapy includes treatment of the acute condition, short-term (pre-procedural) and long-term prophylaxis [5].

Plasma or recombinant C1-INH concentrate therapy replaces deficient/dysfunctional protein in patients with HAE I or HAE II. Exogenous C1-INH concentrate acts on the same targets as endogenous C1-INH. For on-demand treatment, only intravenous administration of C1-INH is effective [7]. Also, the management of patients with HA involves short-term (pre-procedural) and long-term prophylaxis, which is the basis for the prevention of HAE attacks.

Short-term prophylaxis is prescribed if the patient has a number of provoking factors (dental, surgical interventions, examinations with mechanical effects on the respiratory tract and gastrointestinal tract, stress factors (exams, tests, interviews). These factors will be individual for each patient. In addition, after surgery, a patient with HAE should be monitored and have access to treatment “on demand” [9].

Long-term prevention of HAE exacerbations (especially if there is a history of laryngeal edema and/or hospitalization) is important in order to achieve complete disease control and improve patients’ quality of life [6, 10].

In recent years, new drugs for long-term prevention have appeared. Their use significantly reduces the frequency of seizures, and many patients have a complete response. To date, the following drugs have been approved for LTP in the case of HAE by the FDA [2, 11]: plasma nanofiltered C1-INH for intravenous administration; plasma nanofiltered C1-INH for subcutaneous administration; plasma kallikrein monoclonal inhibitor for subcutaneous administration lanadelumab; kallikrein inhibitor – berotralstat, which is an oral drug; anabolic androgens, which are the second line of therapy (danazol and stanozolol); antifibrolytics (tranexamic acid) – the use of this group is possible in the absence of access to first-line drugs and contraindications to the use of androgens [11].

It should be noted that plasma nanofiltered C1-INH is the only first-line drug available in Ukraine for LTP HAE. Since its use requires medical support and control of intravenous administration, the Hereditary Angioedema Standards of Care 2023 [Standard] provide clear criteria for use.

During the treatment of HAE, it is recommended to monitor the patient's condition (anamnesis, laboratory parameters). A diary has been developed for a patient with hereditary angioedema, which provides available information about the disease, main symptoms, key laboratory parameters for verifying the diagnosis, as well as help with an attack of HAE, travel planning tips [10, 11].

It is important that the patient focuses on individual triggers, warning signs, symptoms that may precede attacks, and also fills out a log of the duration, frequency of attacks and location of edema (description of the angioedema attack in the diary).

**Clinical case**

Written informed consent was obtained from the patient reported in the study.

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Patient O., born in 1997 (27 years old), consulted an immunologist with complaints of periodic pain in the abdomen, local swelling of the mucous membrane of the gums, facial skin after visiting the dentist, cracks and wounds on the skin after contact with cold, the appearance of folds in places of pinching clothes.

From the anamnesis of the disease, it is known that in 2013 acute abdominal pain first appeared. Since then, the patient has noted abdominal pain syndrome, which was interpreted as an exacerbation of gastroduodenitis or "acute abdomen", which bother at intervals of 1-2 times a year. In addition, there were weekly sensations of bloating, abdominal cramps.

In 2018, the patient was consulted by a surgeon who referred her to a gastroenterologist, fibrogastroduodenoscopy (FGS) was performed, as a result of which swelling of the soft tissues of the gastrointestinal tract occurred. Due to the frequent interpretation of the patient's complaints by various specialists as manifestations of psychosomatic syndrome, in 2020 she underwent a course of psychotherapy.

During the second FGS in 2022: there was a feeling of lack of air, a "lump in the throat", which was interpreted as a panic attack. In 2022, the patient was consulted by a spinal neurosurgeon: Spina bifida L5, lumbalgia. A course of NSAIDs was prescribed and a blockade was performed, after which edema of the lower extremities occurred. A consultation with an allergist was held in 2023: "Cold allergy", referred for additional examination for HAE. In 2023, the patient was diagnosed of HAE type II at the Regional Center for Allergology and Clinical Immunology, Lviv.

Life history: The patient is from the first pregnancy, the mother was not registered with the gynecologist, there is no data on the course of pregnancy.

Vaccination status: vaccinated according to the vaccination schedule up to 16 years of age. After the introduction of vaccines, abdominal pain syndrome was observed, on the Mantoux test, swelling at the injection site occurred from the age of 15.

Hereditary anamnesis: burdened – mother and grandmother have periodic swelling of soft tissues, did not go to the doctors.

Stigmas: nonunion of the L5 arch of the vertebra Spina bifida, two-horned uterus.

Bad habits, including smoking denies.

Objective data at the time of examination: RR: 18/min, SpO2 - 98% HR: 78 bpm, BP 120/80 mm Hg., T: 36.6°C. The skin is pale, dry, acrocyanosis. There are polymorphic rashes, cracks and wounds on the hands (Fig. 1).

Figure 1. Rash on the dorsal surface of the right hand of patient O., provoked by the cold factor
The mucous membranes are of normal color, there is a local swelling of the mucous membrane of the gums. The rib cage moves symmetrically on both sides. Auscultatory: respiration is vesicular. Heart tones are sonorous, rhythmic, additional murmurs are not detected.

Laboratory examination.

Microbiological examination of pharyngeal secretions: Neisseria sicca – 5.0 x 10^6 CFU/g; Streptococcus viridans – 5.0 x 10^6 CFU/g; Staphylococcus aureus – 1.0 x 10^1 CFU/g – in this amount is the normal microflora of the mucous membranes and skin. Virological examination: Herpes human virus 6 (PCR) (quantification) oropharyngeal swab - not detected; Herpes human virus 7 (PCR) (quantification) oropharyngeal swab – 2.78·10^3 IU/ml IU/ml; Cytomegalovirus (PCR) (oropharyngeal swab, saliva) (quantified) – not detected; Epstein-Barr virus (PCR) (quantification) oropharyngeal swab 2.6·10^4 IU/ml; Epstein-Barr virus (PCR) (quantification) saliva 6.69·10^6 IU/ml. Lymphocyte phenotyping: T lymphocytes (CD45+CD3+) -77.5%; T-helpers (CD45+CD3+CD4+CD8-) 45.9% ; T-cytotoxic cells (CD45+CD3+CD4+CD8+) -26.4%, CD4:CD8 ratio - 1.7; NK-cells (CD45+CD3+ CD16+56+) - 5.0%; B-lymphocytes (CD45+CD19+) -10.5%; circulating immune complexes (medium) – 72 ODU (<55); circulating immune complexes (small) - 172 ODU (<115);

Immunoglobulin A (IgA, serum) 1.15 g/l; Immunoglobulin M (IgM, serum)1.37 g/l; Immunoglobulin G (IgG, serum) 10.91 g/l; Immunoglobulin E (total IgE, serum) 31.8 IU/ml; Complement (C3 component) 0.82 g/l ↓ (N 0.9-1.8)

Complement factor C4 -0.14 g/l (N 0.02 - 0.36)

C1-esterase inhibitor concentration 0.23 mg/l (N 0.16 - 0.33)

C1-esterase inhibitor activity 68 % ↓ (N 70 - 130)

An individual care plan has been developed for the patient, discussed with the patient and available to a multidisciplinary team. Lifelong replacement therapy with a plasma nanofiltered C1-INH is recommended. Currently, the patient receives prophylactic treatment for a year with the drug of the plasma nanofiltered C1-INH 1000 IU, IV slowly, over 10 minutes, twice a week, as well as when necessary. The above-mentioned symptoms decreased, despite the fact that the patient visited the dentist twice and was re-blocked.

The patient was referred for genetic testing.

Thus, the clinical case demonstrates the importance of knowledge about the types of HAE (clinical manifestations, possible triggers, diagnostic criteria) of doctors of various specialties for the timely referral of such patients to an immunologist, allergist.

Discussion

Hereditary angioedema is a potentially life-threatening genetic disorder characterized by recurrent episodes of angioedema. HAE patients had several hospital contacts due to swelling attacks during the years before their diagnosis was established, and half of them consulted a dermatologist. HAE has a significant impact on health-related quality of life (HRQoL) in patients of all ages. Our data provide further insight into an unmet medical need of HAE patients, namely the low number of HAE patients who self-medicate. For many years, only emergency treatment was available to stop a life-threatening angioedema attack.

The HAE treatment landscape is changing rapidly, as new therapies recently made available and others currently under development promise to improve the management of the disease, while providing patients with more convenient administration and greater treatment flexibility. A shift in treatment paradigm, from acute treatment to long-term prophylaxis, is encouraged and expected. By preventing acute episodes of HAE, prophylaxis can help patients avoid needless medication and surgical procedures. It can also reduce the number of hospitalizations and time off work/school.
In conclusions:
1. Hereditary angioedema is a rare genetic disease in which early diagnosis, timely treatment, short-term and long-term prevention provide modern management of such patients, improve their quality of life and level of mental health.
2. A temporary decrease in C1-INH function is periodically detected in women who are carriers of factor XII defect (F12 - c.983C>A; p. (Thr328Lys)) with angioedema attacks caused by estrogen intake or pregnancy.
3. After analyzing the clinical case, the patient has a burdened hereditary anamnesis, she was not pregnant at the time of the examination, did not take estrogens, therefore, in order to finally exclude the defect of factor XII, the results of genetic studies are expected.
4. Identification of HAE variants may be important for diagnosis in symptomatic patients, as well as those with AAE-C1-INH biological features or autoimmunity and no family history.

References