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CLINICAL CASE OF HEREDITARY ANGIOEDEMA TYPE I WITH ATYPICAL COURSE IN ELDERLY PATIENT

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Introduction. The article discusses the issue of diagnostics of Hereditary Angioedema (HAE) Type I and the impact of progress achieved in the diagnosis of this rare disease and the development of treatment methods.

Goal – to discuss the difficult diagnosis of HAE and the impact of the progress in the diagnosis of this rare disease.

Research materials and methods. The material was a clinical case of HAE in a 70-year-old patient with a diagnosis of HAE using modern diagnostic methods.

Clinical case. We report a clinical case that reflects the features of the course of the disease, the clinical manifestation of HAE at an advanced age and the complicated diagnosis of the disease in a 70-year-old woman. Based on clinical data and the results of the conducted study (significantly reduced levels of the C4 complement component, and significantly reduced concentration and activity of C1-inhibitor), the patient's condition was consistent with HAE, Type I. After starting treatment following the immunologist's recommendations, which began in February 2024, the patient's condition stabilized with instances of edema syndrome occurring 1–2 times per month with mild intensity.

Discussion. The most significant obstacle to diagnosing HAE in primary care clinics and emergency units is the low initial suspicion. The clinical manifestations of the disease, whether in the form of skin or submucosal swelling or abdominal pain, are often confused with other conditions, which can significantly delay the diagnosis. In the reported clinical case, it took 2 years to establish the diagnosis. However, a high number of hospitalisations, two surgeries, numerous incorrect and unsubstantiated diagnoses, as well as unnecessary tests and invasive procedures come to the forefront. A particular feature of this clinical case is the late onset of the disease at the age of 70, which is uncommon for HAE.

Conclusions. Physicians of various specialties should be aware of hereditary angioedema to ensure early detection and referral of patients to immunologists.

Keywords: clinical case, hereditary angioedema, C1 esterase inhibitor, elderly, atypical course.

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КЛІНІЧНИЙ ВИПАДОК СПАДКОВОГО АНГІОНЕВРОТИЧНОГО НАБРЯКУ І ТИПУ З НЕТИПОВИМ ПЕРЕБІГОМ У ХВОРОЇ ПОХИЛОГО ВІКУ

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У статті розглянуті питання складної діагностики спадкового ангіоневротичного набряку (САН) та прогрес, який досягнутий у діагностиці та лікуванні хвороби. Проаналізовано клінічний випадок САН у 70-річної пацієнтки із встановленим діагнозом за допомогою сучасних методів діагностики. Виявлено особливості перебігу САН у пізньому віці та ускладнену діагностику хвороби у жінки. Після початку лікування стан пацієнтки стабілізувався, рідше випадки набрякового синдрому легкої інтенсивності. Значною перешкодою для діагностики САН є низька початкова підозра. Клінічні прояви захворювання у вигляді набряку шкіри чи підслизової оболонки або болю в животі часто плутають з іншими станами, що може значно затримати встановлення діагнозу.

Висновки. Лікарі різних спеціальностей повинні знати про САН, щоб забезпечити раннє виявлення та направлення пацієнтів до імунологів.

Ключові слова: спадковий ангіоневротичний набряк, клінічний випадок, інгібітор С1 – естерази, похилий вік, нетиповий перебіг.

Introduction. Hereditary angioedema (HAE) is a rare, potentially life-threatening condition characterized by recurrent swelling of the skin and mucous membranes. The clinical presentation of HAE was first described by

Quincke, and in 1888, Osler identified the autosomal dominant inheritance pattern of the disease.

The original name of the disorder – "angioneurotic edema"– reflected the belief that the condition arose from neurosis. However, over the past 40 years, it has been established that the underlying cause of HAE is a deficiency of functional C1 inhibitor, a protease inhibitor from the serpin superfamily (serine protease inhibitors), with bradykinin being the biological mediator of the edema. In 2000, HAE with normal levels of C1 inhibitor was described, and its molecular mechanisms are still being investigated [2; 4; 14].

HAE is a rare autosomal dominant genetic disorder with a prevalence of 1 case per 50.000 people. The main cause of HAE is a genetic defect in the synthesis and/or function of C1 esterase inhibitor (C1-INH) in the complement system, which is why HAE is considered a primary immunodeficiency.

The primary dysfunction in HAE is the deficiency of functional C1 inhibitor (due to a mutation in SERPING1 – serpin family G member 1/serine protease inhibitor, which encodes C1-INH). C1-INH regulates the activity of multiple proteases involved in the complement system and plasma contact system, as well as in coagulation and fibrinolysis processes. Within the contact cascade, C1 inhibitor inactivates plasma kallikrein, factor XIIa and factor XIIf by acting as a "molecular decoy." When the Arg444–Thr445 bond in the reactive loop of the molecule is cleaved, a conformational change occurs, irreversibly trapping the protease within the C1 inhibitor molecule. As a result, a thermodynamically stable C1 inhibitor–protease complex is formed [2; 14].

C1-INH typically manifests in the 1st or 2nd decade of life. Symptoms can occur spontaneously, but in approximately 50% of patients, they are triggered by provoking factors such as psychological stress, minor trauma (e.g., dental procedures), menstruation, pregnancy, the use of certain medications (e.g., oral contraceptives, ACE inhibitors) and infections. Most patients experience prodromal symptoms, including mood swings, anxiety and fatigue.

Recurrent episodes of skin swelling (asymmetrical, disfiguring, non-pitting after pressure, without itching), without urticaria or a tendency for spontaneous resolution and/or pronounced abdominal symptoms (pain and swelling of the intestinal walls), should prompt the physician to consider HAE. An important aspect of the disease course is also the lack of response to antihistamines and glucocorticoids.

Despite the fact that skin and abdominal episodes are the most common signs of HAE, patients may rarely experience swelling of the genitals, bladder, muscles or joints.

The frequency of laryngeal edema is approximately 0.9% of all attacks; however, all patients with HAE are at risk of developing laryngeal edema, which occurs in more than 50% over a lifetime. A fatal episode of laryngeal edema may be the first manifestation of the disease. Trauma to the oral cavity caused by dental procedures can trigger oral swelling and increase the risk of angioedema of the throat and/or airways [1; 14].

The severity of HAE manifestations can fluctuate throughout a patient's life and vary in severity among members of the same genetic lineage. Early onset of the disease may be associated with a more severe course. If HAE is suspected, the patient should consult an immunologist.

To diagnose HAE, it is necessary to determine the level of the C4 complement component, the level of C1-INH, and the function of C1-INH in serum/plasma according to international guidelines (WAO/EAACI, 2017; The International/Canadian Hereditary Angioedema Guideline, 2019; US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema). It is the function of C1-INH that is reduced in most patients with HAE. HAE is classified into types associated with C1-INH deficiency/reduced activity: Type I – reduced concentration of C1-INH (due to an autosomal dominant inheritance mutation or a new mutation); Type II – reduced activity of C1-INH with normal C1-INH concentration. Very rarely, HAE is associated with a mutation in factor XII (autosomal dominant inheritance) and HAE with unknown etiology (manifesting in families, mutation unknown).

At the beginning of 2023, a clinical guideline titled "Hereditary Angioedema" was published (State Enterprise "SEC MOH of Ukraine," 2022). On January 26, 2023, the standards for medical care for "Hereditary Angioedema" were approved by the Order of the Ministry of Health of Ukraine No. 159. These documents contain systematized provisions developed using evidence-based medicine methodology. They are advisory documents presenting the best global medical practices for managing HAE. However, it should be emphasized that during the diagnosis of HAE with C1-inhibitor deficiency, it is crucial to maintain a high level of vigilance regarding this diagnosis [5; 11].

Goal – to discuss the difficult diagnosis of HAE and the impact of the progress achieved over the last decade in the diagnosis of this rare disease and the development of targeted therapies with the expected reduction in mortality and improvement in the quality of life of patients. The following clinical case demonstrates the pronounced positive effect of new approaches to diagnosis and treatment in clinical practice.

Research materials and methods. The material was a clinical case of HAE in a 70-year-old patient with a diagnosis of HAE using modern diagnostic methods, namely the determination of complement factor C4, C1-esterase inhibitor: concentration and activity. This study was conducted in compliance with the international principles of the ethical code.

Clinical case. We report a clinical case that reflects the features of the course of the disease, specifically the clinical manifestation of HAE at an advanced age and the complicated diagnosis of the disease in a 70-year-old woman.

The 72-year-old woman A. visited an allergist on September 22, 2023, complaining of periodically occurring swelling in the facial area, intermittent paroxysmal abdominal pain accompanied by loose stools, nausea, vomiting and sometimes a drop in blood pressure to 40/0 mmHg and loss of consciousness.

Medical history. The patient has been ill since September 2021, when she began to notice episodes of general weakness. Subsequently, paroxysmal abdominal pain occurred with a frequency of once a month, sometimes accompanied by a drop in blood pressure to 40/0 mmHg and loss of consciousness. Due to the development of the

described symptoms, the patient was repeatedly hospitalized in the surgical unit or in the Intensive Care Unit (ICU), and after a few days, she noticed swelling in the facial area, lasting 2–3 days, resistant to treatment with antihistamines and glucocorticoids. Usually, the onset of episodes was marked by attacks of pronounced general weakness.

Family history. The patient's nephew died suddenly at the age of 36 from unknown causes. Genetic testing of relatives was not conducted.

On February 24, 2022, during the next attack with abdominal pain syndrome, laparoscopic cholecystectomy was performed. During the subsequent attack, the patient presented with abdominal pain, diarrhea and general weakness accompanied by a drop in blood pressure, and was treated in the surgical unit from March 3, 2022, to March 11, 2022. The diagnosis was established as acute mesenteric thrombosis. The following surgery was performed: lower midline laparotomy, revision, sanitation and drainage of the abdominal cavity. In the postoperative period and throughout the next year, swelling was not a concern; however, the frequency of abdominal pain syndromes increased to once a week. Starting in 2023, the abdominal pain attacks decreased, but swelling in the facial area appeared with a frequency of once a month. The ineffectiveness of antihistamines was noted, while the effect of diuretics and glucocorticoids was partial.

The patient was hospitalized 13 times between 2022 and 2023. February 24–25, 2024 cholelithiasis: Acute calculous cholecystitis. March 3–11, 2022: Acute mesenteric thrombosis. April 5–7, 2022: Chronic pancreatitis, exacerbation stage. April 23–27, 2022; May 6–9, 2022; May 10–13, 2022; May 16–19, 2022; July 23–26, 2022: Chronic ischemic abdominal syndrome, painful form. May 28 – June 8, 2022: Crohn's disease? August 11–12, 2022: Acute pancreatitis. February 18–21, 2023; April 27 – May 2, 2023; June 1–5, 2023: Allergic reaction, constantly recurring, of unknown etiology.

During her hospitalization, the patient underwent clinical and laboratory tests, including CBC, biochemical blood analysis, coagulation profile, blood glucose, cortisol, ceruloplasmin, tumor markers HE4, CA125, ROMA – all within normal limits; antibodies to syphilis, HBsAg, HCV; antibodies to H. pylori – negative; stool examination, stool for dysbiosis – normal, stool for FOB – negative. Testing for D-dimer was conducted, which was significantly elevated. May 4, 2022: 1272 ng/mL (N 0-260); August 22, 2022: >10 mg/mL (N<5). Total Ig E: 4.71 IU/mL.

Additional instrumental examination methods. Abdominal ultrasound repeatedly showed signs of ascites and heterogeneous pancreatic tissue. Ultrasound of the lower extremity vessels, carotid arteries, abdominal organs and esophagogastroduodenoscopy – no significant findings. Echocardiogram revealed fibrous changes in the aortic and mitral valves, increased load on the right heart chambers and slight pulmonary hypertension. Ejection fraction (EF) – 57%. Pulmonary artery angiography with intravenous contrast (May 11, 2022) revealed signs of pneumofibrosis. CT scan of the abdominal cavity (January 12, 2022) with intravenous contrast revealed moderately pronounced fatty liver (hepatic steatosis), moderately pronounced hepatomegaly; chronic calculous cholecystitis, bilateral adrenal hyperplasia, numerous cysts in both kidneys and a small amount of pelvic ascites. CT scan of the abdominal cavity and retroperitoneal space with intravenous contrast (April 29, 2022) revealed hepatomegaly due to the left lobe, liver cyst, kidney cysts, calculi in the right kidney, with limited effusion in the small pelvis. CT scan of the abdominal cavity and retroperitoneal space with intravenous contrast (June 16, 2022) showed no signs of mesenteric vessel thrombosis, calculi: small stones in the right kidney, dilation of the right ureter, kidney cysts.

The patient was counselled by specialists as indicated: counselling by a vascular surgeon at the O. O. Shalimov National Institute of Surgery and Transplantation in Kyiv (June 15, 2022): Abdominal ischemic syndrome? An examination was prescribed along with symptomatic treatment. Counselling by an endocrinologist at the State Institution "V.P. Komisarenko Institute of Endocrinology and Metabolism" in Kyiv (June 15, 2022): Abdominal ischemic syndrome.

After evaluating all the data from the medical history, physical examination and previous tests, the study was conducted following the counselling with the allergist.

Immunologic blood test made on September, 26, 2023 showed hemoglobin 131 g/L, leukocytes 7.27x10^9/L, eosinophils 0.07x10^9/L (1%), basophils 0, band neutrophils 0.07x10^9/L (1%), segmented neutrophils 4.0x10^9/L (56%), monocytes 0.36x10^9/L (5%), lymphocytes 2.5x10^9/L (34%), erythrocyte sedimentation rate (ESR) 28 mm/h, absolute lymphocyte count 2482 (800–3600), 34% (19–37); T –lymphocytes (CD2, CD3) absolute count 918 (600–1600), 37% (40–60); (CD4) absolute count 500 (400–800), 20% (30–40); T–killers (CD8) absolute count 350 (200–400), 14% (15–20); Immunoregulatory index (CD4/CD8) 1.4% (2.0–3.0); B –lymphocytes (CD22) absolute count 675 (200–400), 27% (15–30); NBT test 0.9; immunoglobulin A 4.84 g/L (1.25–2.5); immunoglobulin M 3.13 g/L (0.65–2.0); immunoglobulin G 5.79 g/L (7.5–18.0); phagocytic index 49% (40–70); natural killers absolute count 175 (7%).

Diagnosis of HAE was made on September, 28, 2023: Complement factor C4 – <0.08 g/L (normal 0.12–0.36); C1– esterase inhibitor concentration and activity: C1 – esterase inhibitor concentration – 101 mg/L (210–380); C1– esterase inhibitor activity – 13% (70–130). Re-examination conducted on 30.10.2023: Complement factor C4 – <0.08 g/L; C1–esterase inhibitor concentration – 109 mg/L; C1–esterase inhibitor activity – 23%. Complement C1q circulating immune complexes autoantibody – 2.96 U/mL (N <20.0).

On October, 3, 2023 the patient was consulted by Professor A. V. Bondarenko, Doctor of Medical Sciences, an immunologist. Diagnosis: Recurrent angioedema caused by C1 complement inhibitor deficiency. The C1-inhibitor deficiency must be differentiated between hereditary (congenital) type 1 angioedema and acquired angioedema.

Based on clinical data (recurrent facial swelling, severe abdominal edema with significant drops in blood pressure) and the results of the conducted study (significantly reduced levels of the C4 complement component, and significantly reduced concentration and activity of C1-inhibitor), the patient's condition was consistent with hereditary

angioedema. Considering the late onset of the disease and the absence of a family history, additional tests were performed to exclude acquired angioedema, including oncological and autoimmune diseases, with CT and MRI scans of the chest, abdominal cavity and head, as well as tumor markers. Additionally, the concentration of C1q circulating immune complex autoantibodies was determined as a differential diagnostic marker for acquired angioedema – the result was negative.

Given the absence of a diagnosed underlying disease that could have caused the development of acquired C1-inhibitor deficiency, despite numerous examinations, and based on the results of a repeat assay for C4 complement component, C1-inhibitor activity and concentration, strong evidence of hereditary angioedema type I was obtained. Therapy was prescribed as part of the angioedema treatment programme.

The patient required dynamic monitoring for oncological diseases. During an acute episode of angioedema, including an abdominal attack, based on life-threatening indications, the patient was prescribed a single intravenous dose of 1000 IU of C1-inhibitor concentrate. This treatment is administered as needed over the course of 6 months, followed by an evaluation of its effectiveness. The patient should have at least two doses of the medication on hand at all times. In the absence of C1-inhibitor concentrate, tranexamic or aminocaproic acid should be administered at a dose of 2 g/day, divided into 3–6 doses. Until C1-inhibitor concentrate is available for long-term prevention, danazol at a continuous dose of 100 mg/day may be used. If there is no C1-inhibitor concentrate available during episodes of laryngeal edema or facial/neck swelling (due to the risk of laryngeal edema) or acute abdominal attacks, single-group fresh frozen plasma should be administered at a dose of 20 ml/kg body weight, or solvent-detergent-treated plasma. Before scheduled surgical interventions (including endoscopic procedures) or dental treatments, a dose of C1-inhibitor (1000 IU) should be administered to prevent the development of an acute episode of angioneurotic edema, or a dose of tranexamic or aminocaproic acid should be taken (though this is a less effective preventive measure). Scheduled vaccinations against hepatitis A and B, as well as annual flu vaccinations, are recommended. If possible, genetic testing for the SERPING1 gene mutation should be performed. ACE inhibitors are contraindicated, as they may increase the frequency and severity of edema.

The patient was diagnosed with hereditary angioedema, Type I. After starting treatment in accordance with the immunologist's recommendations, which began in February 2024, the patient's condition has stabilized, with instances of edema syndrome occurring 1–2 times per month with mild intensity. The level of D-dimer in the blood was within normal limits. Before triggering events, such as ophthalmologic surgery, prophylaxis is carried out according to the standards and recommendations of the immunologist.

Discussion. Given the prevalence of HAE, which is approximately 1 per 50.000 people, it can be assumed that there are at least 800 people in Ukraine who do not know about their disease and do not receive the necessary treatment [6]. To date, almost 100 people in Ukraine have been diagnosed with HAE. Therefore, the identification, monitoring and administration of up-to-date treatment remain a relevant focus for the medical community in Ukraine [6; 11].

HAE is a rare disease, and awareness of its symptoms and diagnosis among the general medical community is low. Over the last years significant progress has been made in approaches to the diagnosis and treatment of this disease [7; 11; 14]. Nevertheless, the diagnosis of HAE is delayed by an average of 8.5 years from the initial manifestation of the disease, although some studies prove that the average delay exceeds 13–20 years [3; 4]. These delays are concerning, given the significant risk of life-threatening laryngeal angioedema in HAE patients. Therefore, timely detection of the problem is the most crucial step in combating this disease.

In the reported clinical case, it took 2 years to establish the diagnosis. However, the high number of hospitalisations (13!), two laparoscopic surgeries, many incorrect and unsubstantiated diagnoses, and unnecessary tests and invasive procedures particularly stand out. Over the course of 6 months, the patient underwent three CT scans of the abdominal and pelvic organs with intravenous contrast. The publications confirm that HAE patients are often misdiagnosed and subjected to unnecessary medical tests and procedures [6; 7; 9].

The most significant obstacle to diagnosing HAE in primary care clinics and emergency units is the low initial suspicion. The clinical manifestations of the disease, whether in the form of skin or submucosal swelling or abdominal pain, are often confused with other conditions, which can significantly delay the diagnosis [1; 7; 11]. A particular feature of this clinical case is the late onset of the disease at the age of 70, which is uncommon for HAE, but individual cases are described in literature [3]. Acquired angioedema (AAE) due to C1-inhibitor deficiency (AAE-C1-INH) is approximately 10 times less common than HAE. The edema results from increased capillary permeability in response to elevated levels of bradykinin, due to low levels of C1-inhibitor antigen (C1-INH-a) and function (C1-INH-f) and (usually) low levels of complement factor 4 (C4), which mimics HAE Type I or II but manifests for the first time in adulthood with no family history, as happened in the case with our patient. These symptoms arise from the breakdown of C1-INH by autoantibodies or its direct consumption by other diseases, rather than from a synthesis disorder.

The publications [13] report that angioedema attacks with low C1-INH levels, predominantly affecting the face and with late onset of symptoms, are strong indicators of acquired angioedema (AAE-C1-INH), even though it is approximately 10 times less common than HAE. The diagnostic delay for AAE is decreasing and becomes even shorter in cases of an underlying hematological disease as a potential cause. The use of acute and prophylactic treatments available for HAE has provided good symptom control in this cohort of AAE patients. Although diagnosing and treating the underlying (malignant) disease remains the primary goal, patients with severe AAE or those who are not considered for treatment of the primary disease can be treated with medications approved for HAE, including long-term prophylaxis, despite the costs and off-label use [13].

Given the above, the patient underwent full diagnostic and differential diagnosis procedures: the level of complement component C4, as well as the level and function of C1-INH, were assessed twice in accordance with international recommendations. Additionally, complement C1q circulating immune complexes and autoantibodies were tested.

A limitation of this study is the absence of genetic testing for the patient, specifically, the identification of the SERPING1 (PAI-1) gene due to social and financial reasons.

An increase in D-dimer levels in the patient was noted during the examination. According to the publications [10], elevated plasma D-dimer levels have been associated with acute attacks of C1-INH-HAE, particularly those involving the submucosal layer, including abdominal attacks, which were characteristic of our patient. D-dimer levels decreased after 7 days of treatment and did not affect the development of thrombotic events. After the initiation of treatment, the patient also showed a consistent normalization of D-dimer levels.

After confirming the diagnosis of HAE, the treatment is prescribed. Over the last decade, treatment options for HAE in Ukraine have expanded. Since September 2020, patients in Ukraine have finally had access to a medication used for the treatment of acute episodes, as well as for short-term and long-term prevention – C1 esterase inhibitor [11; 14].

This progress has made it possible to treat large populations in a controlled manner, taking into account modern treatment standards and in accordance with European guidelines [5; 8;12]. The goal of HAE treatment is to improve patients' quality of life not only by reducing the frequency and severity of episodes, but also by providing easy-to-use therapy with minimal side effects

A significant advancement in preventive care for HAE has been the approval of subcutaneous treatment methods, including plasma-derived C1-inhibitor and lanadelumab, a human monoclonal plasma kallikrein inhibitor. The better disease control achieved through these treatment methods brings closer the objective of normalizing patients' lives.

A more advanced understanding of the pathophysiology of edema in HAE has led to the development and approval of four medications for use on demand in the treatment of HAE. These include plasma-derived C1-inhibitor, recombinant human C1-inhibitor, bradykinin B2 receptor inhibitors, and plasma kallikrein inactivators. Randomized controlled trials have demonstrated that all of these medications are effective and safe for treating HAE with C1-inhibitor deficiency [2].

Short-term prophylaxis for HAE with C1-inhibitor deficiency may be indicated before medical, surgical or dental procedures, as well as in response to stress-inducing factors (such as exams or interviews), business trips or travel, which can be triggering factors for edema.

It is advisable to prefer the C1-inhibitor, which should be administered 1–12 hours (ideally no later than 2 hours) before the procedure.

In the event that the plasma-derived C1-inhibitor is unavailable, fresh frozen plasma (2 units administered 1–12 hours before the procedure) or attenuated androgen (danazol at a dose of 400–600 mg per day for 5–7 days prior to surgery) can be used. Icatibant, ecallantide and recombinant human C1-inhibitor are not recommended as short-term prophylactic agents due to their shorter half-life [1; 2].

In the past, patients with HAE often experienced anxiety, depression and difficulties in work, education and daily life. A deeper understanding of the pathophysiology of HAE and the classification of its phenotypes have helped to develop new targeted approaches for treating this condition [2; 4]. On-demand treatment has significantly enhanced patient safety and quality of life. Effective and safe prophylactic treatment for HAE is the ticket to the future. A shift in the therapeutic paradigm towards broader prevention is anticipated, which should reduce patients' fear of painful, disfiguring, or even life-threatening attacks.

Conclusions. Physicians of various specialties should be aware of hereditary angioedema to ensure early detection and referral of patients to immunologists, who carry out the diagnosis of this condition, prescribe treatment, and implement preventive measures.

Interdisciplinary collaboration and management of patients by a multidisciplinary team of specialists are key to providing quality medical care for patients with HAE. The team should include general practitioners/family medicine physicians, pediatricians, therapeutists, allergists, otolaryngologists, dentists, gastroenterologists, surgeons, dermatologists, pulmonologists, endocrinologists, rheumatologists, hematologists, oncologists, infectious disease specialists, neurologists, and obstetricians-gynecologists. With proper and timely diagnosis and appropriate management and treatment, the next generation of patients with HAE will view their condition differently – not as catastrophic and life-threatening, but as manageable and safe.

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