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CASE REPORT

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HEREDITARY ANGIOEDEMA. DIAGNOSIS IN AN ASYMPTOMATIC ELDERLY WOMAN

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Abstract Hereditary angioedema (HAE) is a rare disease with an autosomal dominant heredity pattern, due to mutations in the gene encoding the C1 esterase inhibitor. The onset of symptoms usually occurs during childhood. Clinically, it is characterized by repeated episodes of angioedema that may affect the skin, abdomen and larynx/pharynx. The occurrence of attacks and their severity are unpredictable and can be fatal without the appropriate treatment. We present the case of an asymptomatic 65-year-old woman, with a history of three adult children diagnosed with HAE. Despite the high probabilities of being a carrier of the mutation, she had not been previously studied. Diagnosis of HAE in a family member would require screening of all at-risk relatives. Early diagnosis is essential to establish a correct and timely therapeutic strategy in order to reduce the morbidity and mortality associated with the disease.

Key words: hereditary angioedema, type 1, asymptomatic, family screening

Resumen ***Angioedema hereditario. Diagnóstico en una mujer mayor asintomática.*** El angioedema hereditario (HAE) es una enfermedad rara, con un patrón de herencia autosómico dominante, debida a mutaciones en el gen que codifica el inhibidor de la C1 esterasa. El inicio de los síntomas suele ocurrir durante la infancia. Clínicamente se caracteriza por episodios recurrentes de angioedema que pueden afectar la piel, el abdomen y la laringe/faringe. La ocurrencia de los ataques y su gravedad son imprevisibles, y puede resultar fatal sin el tratamiento apropiado. Presentamos el caso de una mujer de 65 años de edad, asintomática, con antecedente de tres hijos adultos con diagnóstico de HAE, quién pese a la alta probabilidad de ser portadora de la mutación, no había sido estudiada previamente. El diagnóstico de HAE en un integrante de la familia obligaría a realizar estudios de cribado en todos los familiares en riesgo. El diagnóstico temprano resulta fundamental para establecer una estrategia terapéutica correcta y oportuna, disminuyendo así la morbimortalidad asociada a la enfermedad.

Palabras clave: angioedema hereditario, tipo 1, asintomático, cribado familiar

Hereditary angioedema (HAE) is an uncommon autosomal dominant disease, with an incidence of 1:10 000 to 1:50 000 inhabitants. It´s characterized by recurrent, self-limited episodes of angioedema involving primarily skin, gastrointestinal track and occasionally the larynx[1-3].

HAE is caused by mutations in the gene that encodes the plasma protein C1 inhibitor (C1-INH)[2]. Two variants of the disease with identical clinical manifestations have been described: Type 1 HAE corresponds to 85% of cases, with low antigenic and functional levels of C1-INH. Type II corresponds to the remaining 15%, with normal antigenic levels, but functionally deficient[1-3]. C1-INH deficiency leads to increasing levels of plasma bradykinin, which, through its binding to B2 receptor in the vascular endothelium, is mainly responsible for the vasodilatation that causes edema[1, 2].

Although the first episode usually occurs during childhood, it may occur at any age[1-3]. Episodes last approximately three days with spontaneous resolution. They may occur at any time without a clear cause, or be triggered by medication, stressful situations, trauma, menstruation or upper airway infections[1-3].

Acute episodes can be treated with C1-INH concentrate (Berinert®); recombinant C1-INH (Ruconest®); kallikrein inhibitor, ecallantide (Kalbitor®) or with bradykinin B2 receptor antagonist, icatibant (Firazyr®)[1-3].Long-term preventive treatment can include: C1-INH concentrate; C1-INH plasma derivative (Cinryze®); lanadelumab (monoclonal antibody plasma kallikrein inhibitor); anabolics with low androgenic activity such as danazol; and antifibrinolytic agents such as epsilon-aminocaproic and tranexamic acids. Finally, for short-term preventive treatment, intravenous C1-INH may be used preferably[2].

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Clinical case

Woman aged 65 with a diagnosis of hypertension and hypothyroidism since the age of 59, was treated with enalapril (5 mg/day) and levothyroxine (75 mcg/day). At the age of 53, a laparoscopic cholecystectomy was performed without complications. She had nine normal pregnancies, seven of which ended in vaginal labor and two in cesarean section. The patient has no other significant case history and doesn´t remember clear episodes of angioedema. She didn´t know her father's medical record and stated that her mother never showed any symptoms of angioedema. She has no information about his seven half-siblings (Fig. 1).

The patient´s 9th children consulted our Unit with a diagnosis of Type 1 HAE for disease follow-up, stating that her parents never showed clear episodes of angioedema. Three out of her eight sibling (C1, C2 and C5) presented symptoms of angioedema. Two of them were studied and diagnosed with HAE (C1 and C5). As well as the asymptomatic children of C1 and C9, the remaining symptomatic sibling (C2) and the five asymptomatic ones hadn´t been studied before (Fig. 1).

Considering the mentioned family clinical history, we suggested to determine plasma levels of C1-INH and C4 in her two children, both parents and in siblings who hadn´t been studied. Her two children and her father were ruled out of the diagnosis under normal results. None of the siblings have performed their studies yet. The mother had low levels of both C1-INH (16 and 14 mg/dl) and C4 (10 and 8mg/dl) confirming diagnosis of Type 1 HAE (reference values of our laboratory; nephelometric technique: C1-INH 20 to 35 mg/dl; C4 16.5 to 38mg/dl). We explained to the patient her diagnosis and suspended enalapril explaining its potential triggering and/or aggravating effect of angioedema. Also, we indicated C1-INH concentrate in case of an attack, and we described that the objective of the symptomatic treatment is to reduce as much as possible the severity and duration of the attacks and to avoid the consequent deterioration of the quality of life.

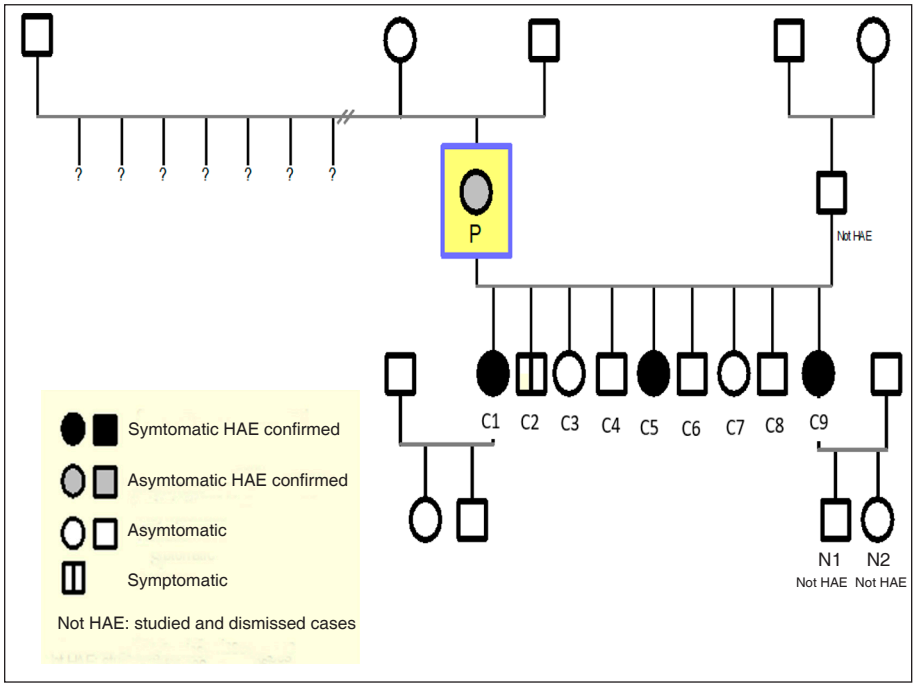
All confirmed cases of HAE in the family are currently on medication for the attacks.

Discussion

HAE is a disease with an autosomal dominant heredity, due to mutations in the gene encoding C1-INH[1]. About 25% of patients present a *de novo* mutation. The rest of them have inherited mutations, so they should have a disease history in their family medical record[1, 2]. Children of patients diagnosed with angioedema are consider to be at-risk individuals with 50% chances of having the disease[1, 2]. In our case, both the patient who came to us (C9) and two of her siblings (C1 and C5) have a confirmed diagnosis of Type 1 HAE, so it is clear that this is an inherited mutation. This means that one of their parents should have the disease, despite being asymptomatic.

In spite of being a hereditary disease, family members of patients with HAE aren´t always evaluated for early diagnosis[4-7]. According to Lunn et al. in a group of 313 patients with HAE, only 48% of the immediate family members had been evaluated[8]. Our patient hadn´t been studied before, even though four of her nine children had symptoms of angioedema and three of them were diagnosed with HAE. Six of her nine children, including a symptomatic

Fig. 1.– Family pedigree. C1: first episode at age 30; skin and abdominal attacks; diagnostic delay: 10 years. C2: first episode at age 32; skin, abdominal and laryngeal attacks; not yet studied (current age: 42 years). C5: first episode at age 30; skin attacks; diagnostic delay: 2 years; first diagnosticated HAE in the family. C9: first episode at age 26; skin and abdominal attacks; diagnostic delay: 2 years



one, hadn´t been evaluated either. It is agreed among the HAE scientific community that all individuals with a positive family medical record of HAE should be considered at risk and studied as soon as the first case in the family is confirmed, whether or not they have symptoms[2, 5, 8-10]. C4 assay is currently the gold standard for screening a patient with suspected HAE, followed by antigenic and functional analysis of C1-INH[11]. Screening of angioedema patient's relatives allows the diagnosis of between 9.8% and 38% of cases that until then were asymptomatic; even in persons over 50, like our patient [4-6, 9, 10].

The diagnostic delay, considered to be the time from the onset of symptoms to confirmation of diagnosis, has decreased in the last few years from more than 20 years, to less than 10 in some reports. The fact that there are asymptomatic patients means that they should be considered as delayed diagnoses: from the moment in which a family member is diagnosed, until the moment of patient diagnosis. Taking this into account, our patient's diagnostic delay could be estimated to be of 8 years.

Affected family members, despite having the same mutation, may have different onset age of symptoms, as well as different affected areas, severity and frequency of attacks[2, 3, 5]. In more than 50% of patients, symptoms onset is before seven years of age and in almost 90% is before 20s[1, 2]. Symptoms onset after 50s is extremely rare, and there are few reported cases over age 65[4, 6, 9]. Although it´s rare that all of our patient's children had late symptoms (after their 20s), what is certainly extraordinary is that she still remains asymptomatic being 65-years-old and having been exposed to events that are widely recognized as triggers for episodes of angioedema, such as surgeries and enalapril intake. On the other hand, it cannot be ruled out that cholecystectomy was an episode of HAE.

Frequency and severity of the attacks are unpredictable. Approximately 50% of patients have at least one laryngeal attack during their lifetime. The chance of a laryngeal attack is almost 1%[2, 7]. Taking this into account, our patient could still have a first episode of angioedema, which, while unlikely, could be laryngeal and life-threatening. Therefore, it was essential to request studies for her diagnosis, and thus inform and provide the medication she should have available for immediate application in case of an attack.

Due to its low incidence, the disease isn´t always known or considered by doctors at the time of diagnosis. Furthermore, since up to 25% of patients have a *de novo* mutation and a late clinical manifestation, suspicion of HAE diagnosis may be difficult. The consequences of undiagnosed HAE can have a direct impact on the patient's mortality in cases of an affected upper respiratory tract. It can also alter the quality of life, due to uncertainty and fear of a possible disease onset. Mortality rate of patients with undiagnosed HAE has been reported to be 31.4%, while that of diagnosed patients is 1.3%[7]. This demonstrates the importance of timely diagnosis with the consequent provision of appropriate medication to treat attacks.

Since HAE episodes are impairing and life-threatening, treatment with locally available medication should be indicated upon diagnostic confirmation[2,5,11-13]. In Argentina, C1-INH concentrate for intravenous application and bradykinin B2 receptor antagonist subcutaneously are available. Patients should always have two doses of a treatment, and at least one of these should be C1-INH concentrate[13]. Whenever possible, patients should be trained in self-administration of medicine[10-13]. It is also necessary to inform about the disease's risks and train the patient's inner circle in medication administration.

Diagnosing at-risk family members reduces the number of unnecessary medical consultations, studies, procedures, treatments, and even surgeries due to misdiagnosis. It allows us to give the necessary information about the disease and indicate treatment. Besides, those with a negative diagnosis alleviate the distressing fear of having the disease.

It is highly likely that the fear in some at-risk individuals prevents the diagnostic studies from being carried out. Probably is what occurred in the described family since the studies were not performed despite having been indicated as extremely important.

A HAE diagnosis in a family member would require screening of all at-risk individuals, regardless of age and presence of symptoms, to identify the disease so as to inform about its risks and future management.

Conflict of interest: None to declare

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A ready man is made by conversation. He that buries himself among his manuscripts, "besprent", as Pope expresses it, "with learned dust," and wears out his days and nights in perpetual research and solitary meditation, is too apt to lose in his elocution what he adds to his wisdom; and when he comes into the world, to appear overloaded with his own notions, like a man armed with weapons which he cannot wield. He has no facility of inculcating his speculations, of adapting himself to the various degrees of intellect which the accidents of conversation will present; but will talk to most unintelligibly, and to all unpleasantly.

A un hombre preparado y listo lo hace la conversación. Aquel que se entierra entre sus manuscritos," espolvoreados", como dice Pope; "con polvo ilustrado", y gasta sus días y noches en perpetua búsqueda y solitaria meditación, está listo para perder en elocución lo que agrega en sabiduría; y, cuando vuelve al mundo, aparece sobrecargado con sus propias nociones, como un hombre armado pero con armas que no puede manejar. No tiene la facilidad de inculcar sus especulaciones, de adaptarse a los varios grados de intelecto en que los accidentes de la conversación se presentaran, su palabra será para la mayoría ininteligible y para todos desagradable.

Samuel Johnson (1709-1784)

The Adventurer, August 28, 1753. No. 85. Study, composition, and converse equally necessary to intellectual accomplishment. In: *https://www.johnsonessays.com/; 5/2/2021*