CASE REPORT

Hereditary Angioedema in Female of Three Generations

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Abstract

Hereditary angioedema type III is a type of angioedema, affecting mainly females, without alteration of the level or function of C1 inhibitor, and is associated with exposure to increased levels of oestrogens. The authors present the case of a previously healthy 14-year-old girl observed with lip and face oedema with four days of evolution. She had started an oral contraceptive about one week before. She had no new episodes of angioedema after stopping the oral contraceptive. In the family history, both the grandmother and great-grandmother had episodes of recurrent angioedema until menopause. The authors intend to discuss a rare form of angioedema with an important impact on the patient's quality of life. The early diagnosis is important and should be based on clinical findings and a detailed family history.

Keywords: Adolescent; Angioedemas; Hereditary; Contraceptives; Oral/adverse effects; Hereditary Angioedema Type III

Introduction

Hereditary angioedema (HAE) is a rare genetic disease affecting approximately 1:50.000 people.[1] It is clinically characterised by episodes of painful, recurrent, non-itching oedema which often affects the face, limbs and several mucous membranes, such as the gastrointestinal or upper airway tracts, with a risk of suffocation and death.[2,3]

Angioedema mediated by bradykinin can be of hereditary origin, and three forms are described[3,4]:

- Type I hereditary angioedema (type I HAE), with reduced levels of C1-esterase inhibitor (C1-INH);
- Type II hereditary angioedema (type II HAE), with normal levels of C1-INH, but decreased function;
- Type III hereditary angioedema (type III HAE), with no change in function or activity of C1-INH. Type III HAE was first described in 2000. C1-INH is a plasma α2-globulin of the serine protease inhibitor family, which acts at different levels, in particular in the complement, fibrinolysis and kinin activation. As it is consumed in the mediated processes, the disease is a consequence of even a single gene mutation.

The clinical manifestations of hereditary angioedema are primarily due to the lower inhibition of the kallikrein function, with increased levels of bradykinin in response to small stimuli with consequent angioedema. C1-INH deficiency will cause the higher activation of the classical complement pathway with decreased C4 and C2 values.[1,2,5] In type III HAE, kallikrein activation is increased without C1-INH involvement, which seems to be dependent on the exposure to increased levels of oestrogen, as in hormone replacement therapy, combined oral contraceptive use or pregnancy. This may justify the fact that these angioedema events occur mainly in female individuals of childbearing age.[1-4] Hence, the condition is also called oestrogen-dependent hereditary angioedema.[3] However, there are some cases of type III HAE described in males.[6] The factor XII (located on chromosome 5) mutation appears to be responsible for 25% of type III HAE cases.[6] At least four mutations leading to the loss of function of this gene are reported. In other cases, the cause is idiopathic.[6-9]

Type III HAE is very similar to other types of hereditary angioedema from a clinical point of view. However, in type III HAE, facial involvement is more frequent, which can be observed in almost all patients, with more than 50% of the cases showing swelling of the tongue and, among these, 25% show laryngeal oedema. On the other hand, only 50% of patients have abdominal pain. The involvement of other organs or the development of erythema *marginatum* is infrequent.[3,6]

Case Report

Fourteen-year-old female, previously healthy, was admitted to the emergency department due to swelling of the lips and face, over the previous four days and

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with no other associated symptoms, including itching, abdominal pain or gastrointestinal changes. The patient was haemodynamically stable, with no airway compromise. She denied any history of trauma or an immediate causal relationship with food or drug intake and had no epidemiological context of infection. She had begun taking a combined oral contraceptive approximately one week before. In her family history, her paternal grandmother and great-grandmother had a history of episodes of recurrent angioedema of the face and limbs associated with combined oral contraceptives and pregnancy. Both family members experienced the complete resolution of the episodes after menopause.

In the physical examination, the patient presented marked swelling of the upper lip and swelling of half the lower lip as well as left hemifacial oedema.

As there was no response to antihistamine treatment, the combined oral contraceptive was discontinued.

In the laboratory studies performed, the C1-esterase inhibitor levels and function and C4 levels were normal (29 and 24 mg/dL, respectively). The patient did not have any new episodes of angioedema.

Discussion

The diagnosis of type III HAE is supported by clinical findings and positive family history. In this case, the presence of symptoms in the paternal female ancestors (grandmother and great-grandmother) and the absence of symptoms in the father are noteworthy and highlight the important role of oestrogen in the pathophysiology. Complementary studies may help distinguish between the multiple subtypes of hereditary angioedema.[7,10,11]

After the diagnosis of HAE is made, the classical complement pathway fractions, C2 and C4, and C1-INH should be determined. If these values are normal, a new determination should be made during a crisis and, ideally, the functional study should be performed, albeit not always easily accessible.[7,10]

Regarding genetic studies, unlike the classic form of HAE, there are multiple genes involved and, therefore, the disease should be considered when the remaining complementary studies are inconclusive, when there is a positive family history and in the context of genetic counselling.[6,7] In this particular case, and despite the positive family history, this study was not conducted as there is no technical possibility for it to be conducted at the time of diagnosis.

The main purposes of treatment for HAE are the reduction of morbidity and mortality, prevention of recurrence as well as the improvement of the quality of life of these patients. This may be subdivided in the crisis treatment and prophylactic treatment.[7]

Therapy with corticosteroids, antihistamines and epinephrine is not effective for HAE,[7,12] as these therapies do not interfere with the blocking of activity or decreased production of bradykinin.

In type III HAE, the standard approach is the discontinuation, to the extent possible, of exposure to oestrogen, such as is the case of combined contraceptives.[7,10,13,14]

Particularly in type III HAE, the indications for different therapeutic options still lack validation by controlled studies. Intravenous C1-esterase inhibitor concentrate, which is the therapy of choice in other forms of HAE, does not seem to have the same efficacy in type III HAE.[12] Icatibant (a bradykinin receptor B2 antagonist) or ecallantide (a selective inhibitor of kallikrein, only available in the United States) may be more appropriate therapies in the acute phase.[7,12-14]

Regarding prophylactic therapy, there is reference to the use of modified androgens (danazol) and antifibrinolytic agents (E-aminocaproic acid and tranexamic acid), for the prevention of crises, but their use is controversial at the paediatric age.[7,12] Cases with favourable response to progestins have also been reported.[7] However, the small number of patients evaluated does not yet allow for a conclusion with certainty of the best pharmacological treatment for type III HAE.

In the present clinical report, a reduction in the exposure to oestrogen consequent to combined oral contraceptive discontinuation was effective, with no need for long-term prophylactic therapy.

Type III HAE is an entity with plenty of unanswered questions, especially regarding its pathophysiology, genetic basis as well as the specific and appropriate treatment. A timely diagnosis and an accurate approach to these cases can be instrumental in decreasing morbidity and improving the prognosis of these patients.

WHAT THIS CASE REPORT ADDS

- The prevalence of the clinical condition and positive family history in the guidance of diagnosis.
- Normal levels of C1-esterase inhibitor and complement do not exclude any form of hereditary angioedema.
- The importance of avoiding oestrogen exposure and the difficulty in a specific therapy of this entity.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Case report presented at the 17th National Congress of Paediatrics, 2017, as a poster and at the European Academy of Allergy and Clinical Immunology Congress 2017, as a poster with discussion.

References

1. Bork K, Barnstedt S, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 2000;356:213-7. doi: 10.1016/S0140-6736(00)02483-1

2. Craig T, Aygören-Pürsün E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J 2012;5:182-99. doi: 10.1097/WOX.0b013e318279affa.

3. Wahn V, Aberer W, Eberl W, Faßhauer M, Kühne T, Kurnik K, et al. Hereditary angioedema (HAE) in children and adolescents: A consensus on therapeutic strategies. Eur J Pediatr 2012;171:1339-48. doi: 10.1007/s00431-012-1726-4.

4. Binkley KE, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000:106:546-50. doi: 10.1067/mai.2000.108106

5. Kaplan AP, Joseph K. Complement, kinins, and hereditary angioedema: Mechanisms of plasma instability when C1 inhibitor is absent. Clin Rev Allergy Immunol 2016;51:207-15. doi: 10.1007/s12016-016-8555-6.

6. Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. Allergy Asthma Proc 2012;33:S145-56. doi: 10.2500/aap.2012.33.3627.

7. Germenis AE, Speletas M. Genetics of hereditary angioedema revisited. Clin Rev Allergy Immunol 2016;51:170-82. doi: 10.1007/s12016-016-8543-x.

8. Cicardi M, Suffritti C, Perego F, Caccia S. Novelties in the diagnosis and treatment of angioedema. J Investig Allergol Clin Immunol 2016;26:212-21. doi: 10.18176/jiaci.0087.

9. Piñero-Saavedra M, González-Quevedo T, Saenz de San Pedro B, Alcaraz C, Bobadilla-González P, Fernández-Vieira L, et al. Hereditary angioedema with F12 mutation: Clinical features and enzyme polymorphisms in 9 southwestern spanish families. Ann Allergy Asthma Immunol 2016;117:520-6. doi: 10.1016/j.anai.2016.09.001

10. Martinho A, Mendes J, Simões O, Nunes R, Gomes J, Castro E, et al. Mutations analysis of C1 inhibitor coding sequence gene among Portuguese patients with hereditary angioedema. Mol Immunol 2013;53:431-4. doi: 10.1016/j.molimm.2012.09.003.

11. Miranda AR, Ue AP, Sabbag DV, Furlani Wde J, Souza PK, Rotta O. Hereditary angioedema type III (estrogen-dependent) report of three cases and literature review. An Bras Dermatol 2013;88:578-84. doi: 10.1590/abd1806-4841.20131818.

12. Cadinha S, Castel-Branco MG, Malheiro D, Lopes I. Protocolo de diagnóstico, tratamento e seguimento de doentes com angioedema hereditário. Rev Port Imunoalergol 2005;13:377-93.

13. Serrano C, Guilarte M, Tella R, Dalmau G, Bartra J, Gaig P, et al. Oestrogen-dependent hereditary angio-oedema with normal C1 inhibitor: Description of six new cases and review of pathogenic mechanisms and treatment. Allergy 2008;63:735-41. doi: 10.1111/j.1398-9995.2007.01579.x.

14. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. Int J Emerg Med 2017;10:1-15. doi: 10.1186/s12245-017-0141-z.

15. LoVerde D, Clark Files D, Krishnaswamy G, et al. Concise definitive review: Angioedema. Crit Care Med 2017;45:725-35. doi: 10.1097/CCM.0000000000002281.