Case Report

Estrogen-sensitive hereditary angioedema type II: a case report and review

Majdy M Qutub

Assistant Professor and Allergist, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
Correspondence to: Majdy M Qutub, E-mail: mmqutub@kau.edu.sa

Received November 18, 2015. Accepted November 25, 2015

Abstract

Hereditary angioedema (HAE) is a rare autosomal condition due to inherited deficiency of C1 esterase inhibitor (C1INH). Estrogen reduces the concentration of C1INH and trigger angioedema; however, the estrogen sensitivity pattern is variable in HAE. Proper diagnosis and management is essential as this condition sometimes becoming life-threatening due to potential airway obstruction. We reported a 27-year-old woman experienced recurrent episodes of lips and face swellings over the last 4 years. Patient has positive family history of similar recurrent angioedema in her brother and cousin. Laboratory findings revealed normal C3, C4, C1q, and C1INH quantity but low activity (36% decreased). Subsequent visits revealed the intake of oral contraceptive pills and improvement of symptoms after discontinuation. To our knowledge, this is the first case report of HAE type II with estrogen-sensitive pattern in a Saudi woman improved after cessation of oral contraceptive pills.

KEY WORDS: Hereditary angioedema, estrogen, CI inhibitor

Introduction

Angioedema (AE) refers to abrupt and short-lived swelling of the skin, mucous membranes, or both including the upper respiratory and intestinal epithelial linings.[1]

AE occurs in 15% of the population and is more common in women than in men.[2] The prevalence of hereditary angioedema (HAE) is estimated to be between 1 in 10,000 and 1 in 150,000.[3] Mutations of non-European origin in *C1NH* gene in HAE patients have been reported in 15 patients of 4 unrelated Arab families in Middle East.[4]

Idiopathic AE is the most frequent form that occurs in 38% of patients and should be considered after a thorough evaluation for other AE syndromes.

AE may be associated with allergic triggers that induce immunoglobulin E (IgE)-mediated symptoms, which begin in minutes to 1 hour after exposure. It is due to the release of histamine from mast cells. It is almost invariably accompanied by urticaria. The common triggers include foods and medications.

AE can be caused by external physical stimuli, such as cold, heat, vibration, trauma, ultraviolet light, and emotional stress, which induce non-IgE-mediated symptoms.

Several drugs are well known to cause AE through a variety of mechanisms. Angiotensin-converting enzyme inhibitors cause AE through effects on bradykinin, whereas other medications, such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), inhibit cyclooxygenase-1 and potentially increase leukotriene production.

Cytokine-associated AE syndrome, also known as episodic AE with eosinophilia or Gleich's syndrome, is characterized by fever, weight gain, elevated eosinophils, and IgM levels in the blood.

Acquired angioedema (AAE) differs from HAE by the absence of a family history of AE and a delayed onset of symptoms, usually in the fourth decade of life or later. Patients have low levels or activity of C1 esterase inhibitor (C1INH), C4, and C1q. AEE occurs in association with lymphoproliferative diseases (AAE type 1) via consumption of the C1INH protein by malignant cells, and in autoimmune conditions, such as systemic lupus erythematosus (AAE type 2), caused by autoantibodies to the C1INH protein.[2]

C1INH is a protease inhibitor acute phase protein. Its main function is the inhibition of the complement system, thus

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2016.18112015208	

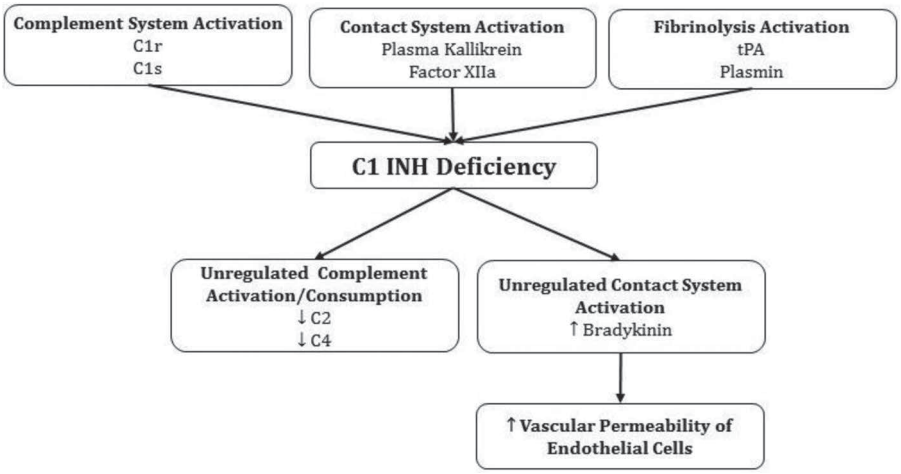

Figure 1: Mechanism of initiation of angioedema attack [Adapted from Davis AE 3rd, Clin Immunol 2005;114(1):3–9].

prevent spontaneous activation. It regulates the activity of the complement component C1, the first step in the classic complement cascade. Furthermore, C1INH has a regulatory role in the contact, fibrinolytic, and coagulation pathways. C1INH deficiency caused by trauma, infection, and other unknown factors as a result leads to unregulated activity of the vasoactive mediators such as bradykinin, kallikrein, and plasmin, which ultimately leads to increased vascular permeability and AE [Figure 1]. Mutations in the gene for this protein cause the autosomal dominant disorder HAE.[5]

In HAE type I, a gene mutation results in decreased plasma antigenic and functional levels of C1INH, which affect 85% of patients. However in HAE type II, 15% of patients have normal plasma C1INH levels but the protein is dysfunctional. Normal expression of C1INH and normal C4 usually rule out HAE types I and II but cannot rule out HAE type III, which is thought to be a mutation in coagulation factor XII gene, which results in increased kinin production. In all types with HAE, swelling episodes occur when inflammation, trauma, stress, pregnancy, medications, or other unknown factors lead to the depletion of C1INH.[6]

The measurement of C4 levels can be performed as a cost-effective screening test to rule out HAE. However, wide range of variability of C4 levels exist, low levels are not uncommon in normal subjects. In patients with C1INH deficiency, C4 levels are markedly decreased although in rare cases, the C4 level is normal between attacks.[7,8] Table 1 summarizes the laboratory evaluation of the C1INH and the complements in AE syndromes.

Case Report

In this case report, a 27-year old house wife with 2 children presented to Samir Abbas Medical Center, Jeddah, Saudi Arabia, complaining of recurrent episodes of face and lips swellings over the past 4 months.

The swelling episodes were recurrent nonpruritic with asymmetric, non-pitting, and non-tender swellings involving face and lips only. History of neither swellings in other body parts nor abdominal pains or tongue or laryngeal swellings was present. She states that she does not have any itching of skin or hives during these swelling episodes. Swelling attacks occur every 3–4 weeks, usually lasts 1–2 days. The swelling attacks were mild-to-moderate in severity without affecting her quality of life or daily activity. She has tried taking over-the-counter medications including diphenhydramine and loratadine, but these did not alleviate her symptoms. The attacks were triggered by upper respiratory infections and emotional stress.

The disease runs in variable manner but in progressive course. The onset of symptoms started in the year 2006 during her first pregnancy in third trimester with swelling of face and lips, which was triggered by upper respiratory infections. Then in subsequent years, the disease runs more progressive course as she developed more than eight episodes of face and lips swellings during her second pregnancy and continued suffering the recurrent swelling episodes thereafter regularly every 4–6 weeks.

The past history of other allergic disease was unremarkable. Patient denied history of any food allergies that could have triggered the swellings. Patient reported history of osteoarthritis of right knee joint for which she underwent arthroscopy. Drug history revealed intake of paracetamol and nonsteroidal anti-inflammatory drugs, hair growth formula for more than 1 year, calcium supplements, and antihistamines. Patient reported similar episodes of recurrent swellings in her brother and first-degree male cousin. Her physical examination was otherwise unremarkable.

Initial laboratory workup showed raised C-reactive protein 7.06 mg/L (normal range: 0–3 mg/L) and total IgE 211.1 IU/mL (normal: <100 IU/mL) [Table 2]. Complete blood count, eosinophil cell count, and tests for specific IgE for common inhalant and food allergens were essentially normal. Thyroid function

Table 1: C1INH and complement evaluation in AE syndromes

AE syndromes	Laboratory results				
	C1INH level	C1INH function	C4	C1q	Gene mutation
HAE type I	↓	↓	↓	N	C1INH
HAE type II	N	↓	↓	N	C1INH
HAE type III	N	N	N	N	Factor XII
Acquired	↓ or N	↓	↓	↓	—
Allergic	N	N	N	N	—
Idiopathic	N	N	N	N	—

AE, angioedema; HAE, hereditary angioedema; C1INH, C1 esterase inhibitor; C4, complement 4 level; C1q, complement C1q level; N, normal level.

Table 2: Results of initial laboratory workup

Test	Result	Reference values
CRP	↑ 7.06	0–3 mg/L
ESR	3 mm/h	0–20 mm/h
Eosinophil count	↓ 0.0	0.04–0.4 K/mL
Total IgE	↑ 211.1	<100 IU/mL

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgE, Immunoglobulin E.

Table 3: Results of specific laboratory tests for diagnosis of hereditary angioedema

Test	Result	Reference values
C3	1.82	0.68–1.32 g/L
C4	0.45	0.14–1.33 g/L
C1q	147	100–250 mg/L
C1INH (quantity)	282	210–345 mg/dL
C1INH (activity)	↓ 28.3 ↓ activity 36%	67.4–93.6 U/mg

C3, complement 3; C1INH, C1 esterase inhibitor.

tests; thyroglobulin antibodies; and immunoglobulins A, G, and M were within normal range.

Patient continued to have recurrent attacks of face and lips swellings, which were worsened during menstrual cycles. This draws attention to ask further drug history, which revealed intake of oral contraceptive pills (OCPs) for years.

Further specific laboratory workup revealed normal complement level (C3 and C4). C1INH was measured by radial immunodiffusion (The Binding Site, Birmingham, UK), C1INH was assayed by functional enzyme-linked immunosorbent assay (Quidel, San Diego, CA). Normal C1INH antigenic protein level but significantly reduced functional level (36% reduced activity) was demonstrated. Serum C1q was within normal range [Table 3].

A diagnosis of HAE type II was established based on clinical and laboratory findings with sensitivity to estrogen hormone as symptoms were triggered and worsened by OCP intake, menstruation, and pregnancy. OCP cessation and alternative birth control method were recommended. AE episodes improved significantly after stopping OCP.

Discussion

In 2003, Bouillet et al.[9] reported five similar patients who developed recurrent AE episodes during the first year or later after starting contraception. All women had normal serum C4 and C1INH antigen levels, but a lowered C1INH activity. The cessation of OCP was associated with marked regression of the symptoms and normalization of C1INH function.

The study by Bork et al.[10] concluded that OCP or hormone replacement therapy can either induce or exacerbate symptoms of HAE or idiopathic AE. However, many women with these diseases found to tolerate these medications without having any effects on their AE.[10]

The estrogen sensitivity is variable in HAE. Three distinctive patterns are known in relation to estrogen sensitivity. HAE type III usually have estrogen dependent pattern and AE occurs only when they are exposed to the OCP or during pregnancy. In estrogen-sensitive pattern the symptoms are worsened by taking OCP medication or during pregnancy. Any type of HAE can present in this pattern. However in estrogen-independent pattern, the use of the OCP or pregnancy does not exacerbate the symptoms.[11]

Careful clinical history to clarify the association of symptoms to menstrual cycles, pregnancy, and intake of oral estrogen has to be stressed in subjects with recurrent AE, as the clinical features and the time-course often suggest the possibility of estrogen-related pattern. Our patient demonstrated remarkable improvement of AE episodes after discontinuation of pills.

Combined contraceptive pills can exacerbate symptoms in 63%–80% of women.[11] Oral estrogens reduce the concentration of C1INH in patients with HAE. Moreover, estrogens can alter bradykinin synthesis and its degradation pathway. Therefore, combined contraceptive pills are contraindicated in patients with HAE. Progestogen-only pills, intrauterine devices, and transdermal hormonal contraceptives are good alternatives. The administration of transdermal estrogens bypass the first hepatic step of estrogen metabolism and has low or null effect on C1INH and bradykinin pathway.[12]

Conclusion

To our knowledge, this is one of the few case reports of HAE type II with estrogen-sensitive pattern in a Saudi woman improved after discontinuation of oral estrogen.

Acknowledgments

Special appreciation and thanks to Prof. Emad Koshak, consultant allergy, asthma, and immunology, and Dr. Mohammed Alrabea, consultant clinical immunologist, for their invaluable assistance and guidance.

References

1. Kaplan AP, Greaves MW. Angioedema. J Am Acad Dermatol 2005;53(3):373–88.
2. Temiño VM, Peebles RS Jr. The spectrum and treatment of angioedema. Am J Med 2008;121(4):282–6.
3. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001;161(20): 2417–29.
4. Faiyaz-Ul-Haque M, Al-Gazlan S, Abalkhail HA, Al-Abdulatif A, Toulimat M, Peltekova I, et al. Novel and recurrent mutations in the C1NH gene of Arab patients affected with hereditary angioedema. Int Arch Allergy Immunol 2010;151(2):149–54.
5. Davis AE 3rd. Short analytical review: the pathophysiology of hereditary angioedema. Clin Immunol 2005;114(1):3–9.
6. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 2010;6(1):24
7. Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. J Allergy Clin Immunol 1986;78(6):1115–20.
8. Zanichelli A. Angioedema due to C1 inhibitor deficiency in 2010. Intern Emerg Med 2010;5(6): 481–6.
9. Bouillet L, Ponard D, Drouet C, Jullien D, Massot C. Angioedema and oral contraception. Dermatology 2003;206(2):106–9.
10. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by OCP or HRT. Am J Med 2003;114(4):294–8.
11. Bouillet L. Hereditary angioedema in women. Allergy Asthma Clin Immunol 2010;6(1):17.
12. Sanhueza PI. Contraception in hereditary angioedema. Fertil Steril 2008;90(5):2015.e21–2.

How to cite this article: Qutub MM. Estrogen-sensitive hereditary angioedema type II: a case report and review. Int J Med Sci Public Health 2016;5:593-596

Source of Support: Nil, **Conflict of Interest:** None declared.