Hereditary Angioedema: Not Just Common Angioedema

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ABSTRACT:
Hereditary angioedema is one of most challenging problems in field of dermatology in term of correct diagnosis and timely management. We present case of a Thai female aged 47- years-old woman form Saraburi province with history of recurrent swelling of extremities after physical injuries with resolved spontaneously within 24 hours; moreover, history of recurrent events of abdominal pain ensued. Swelling of facial, eyelids, lips, tongue, and genitalia had occurred frequently. Upper airway obstruction also presented and severe enough to incur hypoxic arrest. Her father passed away from upper airway obstruction. Her 13-year-old son also had suffered from recurrent episodes of angioedema and abdominal pain. Her blood samples were investigated. Apart from her first visit, her C4 level is between 11.2-12.7 mg/dl, showing persistently low level (normal C4 complement level: 14-44 mg/dl) regardless of her disease status. Her C1 inhibitor is 7.7 mg/dl (normal C1 inhibitor: 19-37 mg/dl), Her C1 activity is 32 percent. She was diagnosed as hereditary angioedema type 1.
Her management included danazol 200 mg orally on alternate day for prophylaxis, icatibant (bradykinin beta 2 receptor antagonist) during an attack, fresh frozen plasma infusion in term of short course prophylaxis, emergency ID card addressing her underlying disease. Her offspring had been investigated and managed promptly
Key words: Hereditary angioedema, angioedema without wheal

Hereditary angioedema is one of the most challenging problems in the field of dermatology in terms of correct diagnosis and timely management. We present the case of a Thai female aged 47 from Saraburi province with a history of unexplained recurrent swelling of extremities after physical injuries. The swelling was not accompanied by a wheal and could resolve spontaneously within 24 hours.

Swelling of the face, eyelids, lips, tongue, and genitalia also occurred frequently. Menstruation, physical injuries, psychological stress, and dental procedure seemed to aggravate it.

Moreover, between age 26 and 30, she had acute abdominal pain, and was sent to laparotomy without any pertinent abnormal intraoperative findings.

The management of the Thai female's case included danazol 200 mg orally on an alternate day for prophylaxis, icatibant (bradykinin beta 2 receptor antagonist) during an attack, fresh frozen plasma (FFP) infusion in terms of short course prophylaxis, and an emergency ID card addressing her underlying disease. Her offspring were also investigated and managed promptly.

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Discussion

The authors present this case in order to scrutinize the importance of early correct diagnosis. The time from presentation to diagnosis in this case is more than twenty years. Hereditary angioedema (HAE) is a rare, challenging, and potentially life-threatening condition[1]. It is characterized by angioedema without association with wheal, mainly due to bradykinin, which is derived from cleaved HMWK. The mechanism is complex, and displays involvement between various systems, including the coagulation system, contact system, and complement pathway. Interestingly, patients who suffer from HAE do not appear to be more susceptible to bleeding or thrombosis[2]. It can be further divided into three subtypes: Type 1 and type 2 HAE both result in reduced effective C1 esterase inhibitors, owing to a mutation in SERPING1, which regulates multiple proteases that play roles in the contact system, coagulation, complement, and fibrinolytic cascade. The mutations that lead to the former type are diverse, including missense, nonsense, frameshift deletion or insertion, or splicing defects scattered throughout the gene[3], resulting in truncated or misfolded C1 inhibitor that is not effectively secreted.

In the latter type, the defect is usually a missense mutation in exon 8, affecting the mobile loop and interfering with the ability to inhibit the target proteases[2]. The mode of inheritance is autosomal dominant with full penetrance; however, twenty-five percent of the mutation occurs de novo. Gene sequencing is not mandatory for the diagnosis but may be required in difficult cases.

In type 3 HAE, also known as HAE with normal C1 inhibitor, the mechanism is believed to be enhanced by bradykinin signaling. The critical step for making a diagnosis of hereditary angioedema is to maintain a high index of suspicion.[4] The symptoms largely come from bradykinin and thus do not respond to mast cell-targeted treatments such as antihistamines, corticosteroids, or epinephrine. A history of multiple events of attacks of cutaneous angioedema that is asymmetric, nonpruritic, without wheal, and/or severe abdominal symptoms without other known underlying diseases should trigger the clinician to consider the probability of hereditary angioedema, as in this patient's case. The patient may have occasionally experienced genital swelling or upper airway obstruction. In this case, she fortunately survived the latter condition. However, the mechanism triggering events is not clearly explained. Moreover, estrogens and angiotensin-converting enzyme inhibitors often worsen the symptoms.

Type 1 and type 2 HAE are both characterized by low levels of serum C4 due to activation of the complement cascade, in which the C1 inhibitor takes part in the process.

Patients suffering from HAE type 1 have low antigen and functional C1 levels, in contrast to type 2 patients who have normal antigen but low C1 inhibitor function. In terms of screening tests, serum C4 level is useful for HAE-C1INH, with sensitivities varying from 81% to 96% between angioedema episodes, and 100% during the attack[3]. Measurement of C1INH protein antigenic and functional levels is necessary to confirm or exclude HAE-C1INH. C1INH quantitative and functional levels are low (<50% of normal) in type I HAE, whereas only the functional level is low (<50% of normal) in type II HAE. In patients with angioedema without wheal after 40 years old, or with concomitant lymphoproliferative or autoimmune disease, a C1q level may be used to distinguish between HAE-C1INH and acquired C1INH deficiency. Once a diagnosis has been made, testing of the patient's parents, siblings, and offspring is highly recommended.

Managing HAE can be categorized into; 1. treatment of acute HAE attacks, 2. long-term prophylaxis, and 3. short-term prophylaxis for anticipated triggers[5]. Plasma-derived and recombinant human C1 inhibitors, bradykinin

B2 receptor inhibitors, or plasma kallikrein inactivators can be used to treat an acute attack. Long-term prevention can be divided into 2 broad categories: first-line and second-line. The first-line therapies include plasma-derived C1INH replacement and a plasma kallikrein monoclonal inhibitor. Second-line therapies include anabolic androgens and antifibrinolytic agents. For anticipated short-term prophylaxis, danazol and FFP can be used in addition to the C1 inhibitor.

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