Hereditary Angioedema: Three Cases Report, Members of the Same Family

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ABSTRACT

Background: This current clinical case report highlights three cases of hereditary angioedema (HAE) patients who are all members of the same family (father and his two daughters). The father has C1–INH deficiency, while his daughters have low C1–INH levels: the first possesses only 10% function and the second has low C1–INH level with 0% function. Of note, the second daughter was discovered to have HAE at the age of 2, thus making her the youngest known HAE case report in the English literature.
Methods: Assess the efficacy of administration of C1-INH before dental operation as regards the prevention of HAE episode, when total or partial C1-INH deficiency exists.
Results: Acute angioedema leading to laryngeal oedema is a possibly fatal complication for HAE patients undergoing dental procedures. Use of both short-term and long-term HAE prophylaxis prior to dental operations might be life saving for those patients.
Conclusions: Prevention and early recognition of potential laryngeal oedema that can occur as a complication of dental procedures may be lifesaving for HAE patients.

Keywords: hereditary angioedema; laryngeal edema; oral surgical procedure; operative dentistry; tooth extraction.

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INTRODUCTION

Hereditary angioedema is an autosomal dominant disease clinically characterized by recurrent face, skin or extremity swelling as well as gastrointestinal concerns and respiratory system failure. Since HAE is not an allergic phenomenon pruritis does not occur concomitant with the swelling [1]. HAE manifestations in the upper respiratory system, specifically involvement of the larynx, may lead to asphyxiation, which is the primary cause of death among HAE patients [2]. There are many known HAE episode triggers, including oral surgical procedures such as tooth extraction. Such episodes can lead to laryngeal oedema, a life-threatening situation [1,2].

HAE is classified into two types of dysfunction: Type 1 HAE is caused by decreased production or absence of C1 esterase inhibitor (C1-INH). Type 2 HAE is characterized by normal C1-INH level indicating functional impairment [3]. Type 3 HAE has been described in female only and presents normal function C1-INH levels [4].

Angioedema was initially described by Milton in 1876 [5]. In 1882 Quincke [6] named the disease "angioneurotic edema" because of the relationship noted between mental stress and disease exacerbation. In 1888 Osler [7] was the first to describe the clinical manifestations of angioedema. In 1963 Donaldson and Evans [8] discovered that C1-INH deficiency was the underlying cause of HAE, thus identifying HAE type 1. This ascertainment was followed by Rosen et al. [9] who in their conclusions described HAE type 2 in 1965.

Another type of angioedema is acquired angioedema (AAE). In 1970 Caldwell et al. [3] described AAE type 1, which is characterized by low C1-INH levels and accompanies conditions including connective tissue diseases, infections, leukemia and some types of cancer. In AAE type 2 C1-INH levels are normal but existing C1-INH autoantibodies lead to C1-INH dysfunction.

CASE DESCRIPTION AND RESULTS

Three HAE cases in one family are described, including the father and two of his daughters.

Case 1. A 56 year old man visited hospital because of an acute abscess of the maxillary right canine. His past medical history was remarkable for C1-INH deficiency that had originally presented when he was twenty years old. He stated that his episodes usually manifested as swellings in his extremities (hands to elbows and feet to knees), and less often in his face and genital organs. He said that the usual duration of his episodes were 2 to 3 days, and that they resolved spontaneously. He denied any episode of laryngeal oedema. Laboratory testing revealed total C1-INH deficiency (Table 1). He mentioned that his father suffered similarly but had refused laboratory testing or treatment. None of his 12 brothers had ever demonstrated HAE symptoms.

Following admission to hospital he was administered 1000 units of intravenous C1-INH and preoperative antibiotic prophylaxis. The tooth extraction was performed on the following day. His convalescence was trouble-free and he was discharged in 3 days.

Case 2. The 18 year old daughter of the father described above (Case 1). She was the first of three children and suffered from cerebral palsy and severe mental retardation. She was admitted to hospital for dental surgery (root extraction). Her initial HAE manifestations were face and upper extremities swelling primarily at age 16, with swelling that progressively increased over the next 10 to 20 hours and lasted two to three days. This was followed by spontaneous regression. Her father reported that she had been admitted to hospital once for dyspnea accompanied by upper extremity swelling.

Her laboratory examination revealed low C1-INH level with 10% function (Table 1). Her regular medication regimen included prophylactic attenuated

Table 1. Patients' serologic parameters levels[a] and their effects on C1-INH concentration[b]

Serologic parameters	First case (father)	Second case (first sister)	Third case (second sister)	Third sister	Mother
IgG	11.8 (8 – 18)	16 (8 – 18)	13.4 (7.9 – 17.7)	12 (7 – 15.1)	13.1 (8 – 18)
IgA	4 (0.9 – 4.5)	3.7 (0.86 – 4.3)	1.7 (0.7 – 3.65)	1.7 (0.45 – 2.3)	1.1 (0.9 – 4.5)
IgM	1.9 (0.6 – 2.5)	4.7 (0.68 – 2.3)	4.0 (0.6 – 2.2)	1.85 (0.6 – 2.2)	2.6 (0.7 – 2.8)
IgE		22 (< 104)	36 (< 104)		
C3	1.1 (0.6 – 1.6)	1.3 (0.6 – 1.6)	1.1 (0.6 – 1.6)	1.3 (0.6 – 1.6)	1.15 (0.6 – 1.6)
C4	0.2 (0.15 – 0.4)	< 0.08 (0.15 – 0.4)	< 0.1 (0.15 – 0.4)	0.25 (0.15 – 0.4)	0.2 (0.15 – 0.4)
C1 INH	(-)	10 % (-)	(-)	(+)	(+)

[a]Serologic parameters levels expressed as mg/ml (range).
[b]C1-INH concentration: (-) = Deficiency C1 INH; (+) = Normal C1 INH.

androgen therapy (Danazol caps 200 mg, a dosage of 400 mg daily). C1-INH was administered preoperatively. Her postoperative course was unremarkable.

Case 3. The otherwise healthy twelve year old second daughter's initial HAE presentation was at age 2. Her usual presentations were extremity swelling following small injuries and injections. In her medical history there were not reported HAE episodes caused by dental procedures. Her HAE episodes usually lasted 2 to 4 days and were followed by spontaneous regression, just like her father and sister. She reported multiple hospital admissions for HAE episodes. Her laboratory examination revealed low C1-INH level with 0% function (Table 1).

Of note, the mother and remaining daughter of the family were both clinically healthy and demonstrated no laboratory evidence of HAE (Table 1).

DISCUSSION

There are many known HAE episode inciting factors, including physical injury, medical or dental operations, psychological stress, menstruation, infections or certain medications – a list that includes contraceptive pills and angiotensin-converting enzyme (ACE) inhibitors [1]. During the acute phase of an HAE episode manifestations may include diffused skin, peptic and respiratory mucosa oedema. Cerebral oedema may also occur, leading to migraine type pain, as well as cerebrovascular incidents [1]. Face oedema may be limited to the eyelids only or may extended to its entire surface, the lips and, rarely, to the oral cavity (tongue and soft palate). The combination of lip swelling in the form of *cheilitis glandularis* and face swelling, which constitute the characteristic clinical findings of Melkersson–Rosenthal syndrome can, during the first stages of its appearance, lead to the mistaken diagnosis of angioedema [2]. A tip for helping differentiate the two is that in the case of *cheilitis glandularis* lip swelling is stable and it is not accompanied by other findings that lead to the diagnosis of angioedema. Gastrointestinal system symptoms are caused by visceral oedema, which include anorexia, nausea/or vomiting and abdominal pain. Also, fluid extravasations into the peritoneal cavity as a result of vasodilatation in HAE may sometimes lead to ascites and fluid imbalance that can lead to hemodynamic shock, which requires aggressive fluid resuscitation to prevent this potentially severe complication. A common presentation of an HAE episode concentrated in the gastrointestinal tract is severe abdominal pain accompanied by nausea or vomiting and is often indistinguishable from an acute abdomen. This can lead to misdiagnosis and unnecessary surgical operations, of which appendectomy is the most common. Gastrointestinal tract attacks usually subside within 12 - 24 hours [1].

Findings similar to those seen in HAE can be observed in patients prescribed ACE inhibitors for hypertension or/and congestive heart failure treatment. The incidence of angioedema in patients taking ACE inhibitors is approximately 0.1% to 0.5%. Distinguishing between HAE and angioedema induced by ACE inhibitors is achieved by reviewing the patient's medical history and their C1-INH levels: Those with ACE-induced angioedema will relate no prior episodes of angioedema, will note that their angioedema did not develop until they were started on an ACE, and their C1-INH levels will be normal. For patients who develop ACE-induced angioedema the issue should resolve with discontinuation of the ACE. The physician then provides the patient an alternative therapy instead of an ACE for the condition being treated [1].

HAE usually presents during the second decade of life but may also appear at other ages. Bork et al. [11], having studied 123 cases of HAE patients, came to the conclusion that first HAE appearance was most frequently seen between 11 to 45 years of age, while the youngest known confirmed case at that time was 3 years old. Interestingly, one of the cases in our case presentation was that of a young girl whose first HAE episode was seen at age 2.

The intervals between HAE crises differ between patients and may also differ in the same patient. Factors that influence frequency of HAE episodes among others depend on motivating factors existence and whether the patient is being prescribed long-term medication prophylaxis.

As stated previously, oedema can affect many body regions but laryngeal oedema constitutes the most worrisome potential symptom of HAE, as it can cause death by asphyxiation [2,10,11]. Life-threatening laryngeal oedema can be an HAE patient's initial presenting HAE symptom, it might follow face or extremity oedema, or it could appear during every episode in a specific HAE patient. Bork and Barnstedt [2] report four fatal laryngeal oedema cases in HAE patients where oedema appeared 4 to 30 hours following tooth extraction. The patients' medical history examination revealed that 3 out of these 4 patients had developed laryngeal oedema for the first time. C1-INH was not administered to any of them either prophylactically or therapeutically a factor that may have contributed to their poor clinical outcomes. Bork et al. [11], after studying 123 HAE patients, concluded that roughly half of them (61 patients - 49, 6%) had experienced one or more laryngeal oedema episodes. When they compared the incidences of laryngeal oedema to skin oedema to

oedema of internal organs, the oedema rate was found to be laryngeal : skin : internal organs = 1 : 70 : 54. They thus concluded that upper airway system attack (larynx) is less common (1 laryngeal oedema in 125 angioedema episodes). Also, they noted that the interval between the initial appearance of laryngeal oedema and its complete appearance ranged from 8 to 12 hours, with the mean time being 8.3 hours (only one patient had laryngeal oedema that appeared in less than 3 hours) [11].

According to the above researchers, factors that increase likelihood of laryngeal oedema in HAE are:

- Preceding dental operation or general anaesthesia (intubation);
- Age between 11 - 45 years;
- Prior, or multiple, laryngeal oedema episodes;
- Prior episode of face oedema (face oedema does not always precede laryngeal oedema).

They also described the following factors that reduce the likelihood of laryngeal oedema in HAE:

- Age under 11 and over 45 years;
- Absence of prior laryngeal oedema episode (one must still keep in mind that a patient could still suffer from a fatal laryngeal episode that was their initial episode);
- Long-term medical prophylactic therapy.

The management of HAE is multifactorial and consists of long-term maintenance/prophylaxis a factor that includes avoidance of situations or activities known to incite episodes in the specific patient, prophylaxis prior to dental or medical procedures (short-term prophylaxis) and, finally, medical management of acute angioedema episodes (acute phase) [12]. If one excludes C1-INH, angioedema prevention measures include attenuated androgen administration (danazol-stanozolol), fresh frozen plasma (FFP), and antifibrogenolytic factors such as E-aminocaproic acid and tranexamic acid. Corticosteroids and antihistamines administration is not helpful in HAE patients.

C1-INH provided before medical and dental procedures is effective in the prevention of angioedema as well as in the management of acute HAE episodes, including laryngeal oedema [10,12-14]. Alternatively, preoperative administration of FFP is recommended, especially in those countries where C1-INH is not available [1,3]. However, FFP administration has two disadvantages: possible transmission of contagious disease, including hepatitis B, C and HIV infection, amongst others, because it is a biological product; and secondly, anaphylactic shock or resurgence of angioedema due to the fact that FFP consists of supplement factors, including C4 [1,3,12].Accordingly, FFP administration is not recommended in acute angioedema episodes because C4 excess caused by FFP can intensify existing oedema [1,3].

For these reasons Turner et al. [15] suggest administration of recombinant plasma kallikrein inhibitor (OX-88) use prior to dental operation in the hopes of preventing bradykinin formation, a factor responsible for angioedema appearance. Conversely, some authors mark the necessity of further clinical studies for evaluating the safety and effectiveness of this factor in both the prophylaxis and acute management of HAE patients [15].

Factors that combat fibrinogenolysis, including E-aminocaprioc acid and tranexamic acid, are used in long-term HAE prophylaxis [2]. These factors impede C1 and plasmin activation [15].

Attenuated androgens (danazol-stanozolol) are the most frequently used prophylactic regimen in the management of HAE. Androgens are clinically proven to reduce oedema occurrence in skin and internal organs as well as abdominal pain [1]. They also reduce both the frequency and severity of laryngeal oedema episodes. Nevertheless, their use is limited due to their numerous and significant side effects, including weight gain, headache, myalgia, hypertension, libido decrease and liver concerns, including hepatic adenomas and hepatic carcinoma. Additionally, side effect concerns specific to female include menstrual disturbances and masculinization (muscle hypertrophy, breast reduction, and deepening of voice). The presence of these possible side effects has resulted in the need for minimal dosing in these populations and the recommendation that children and young female be excluded from using attenuated androgens as a prophylactic regimen in their HAE management strategy [10].

Administration of C1-INH factor is effective in both dental and medical procedural prophylaxis and treatment of acute HAE episodes, including laryngeal oedema [10]. Studies have revealed that failure to administrate C1-INH on laryngeal oedema was fatal to patients. Also, because HAE is not an allergic condition, corticosteroid and antihistamines administration does not constitute an effective therapy [2].

Finally, the importance of educating patients and their relatives about the disease and its potentially severe complications, including acute laryngeal oedema, cannot be stressed highly enough. Patients must truly understand that the best way to prevent possibly avoidable loss of life from laryngeal oedema is early recognition followed by presentation of the patient for emergency care.

CONCLUSIONS

Prevention and early recognition of potential laryngeal oedema that can occur as a complication of dental procedures may be lifesaving for HAE patients.

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