Hereditary angioedema
a mother diagnosing her child using Google as a diagnostic aid
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Published in:
BMJ Case Reports

DOI:
10.1136/bcr-2018-225825

Publication date:
2018

Document version
Accepted manuscript

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Citation for published version (APA):

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Hereditary angioedema: A mother diagnosing her child using Google as a diagnostic aid.

Hereditary angioedema (HAE), due to C1-inhibitor deficiency, is a rare autosomal dominant and potentially life-threatening disease characterized by recurrent edema attacks of skin, mucosa and viscera. Due to the rarity and the fact that symptoms of HAE imitate other forms of angioedema and other conditions, HAE may be misdiagnosed, especially in emergency settings. Consequently, HAE patients may experience significant delays in diagnosis. Without an accurate diagnosis HAE patients may not receive proper treatment. At times 'Doctor Google' may be an important tool in establishing the diagnosis. The aim of this case report is to emphasize the importance of listening to patients and relatives and being humble to 'Doctor Google'. Furthermore, the aim is to remind all health care personal of HAE and its importance of considering the rare differential diagnoses to common symptoms.

Hereditary angioedema (HAE), due to C1-inhibitor (C1-INH) deficiency, is a rare autosomal dominant and potentially life threatening disease characterised by recurrent oedema attacks of skin, mucosa and viscera [1]. Attack triggers may include stress, menstruation, oral contraception and pregnancy [2,3]. Delayed treatment of laryngeal swelling can result in death [4,5]. HAE is caused by mutations in SERPING1 which encodes C1-INH and result in quantitative deficiency of C1-INH (type 1) or dysfunctional (type 2) of C1-INH protein.

Due to the rarity and the fact that symptoms of HAE imitate other forms of angioedema and other conditions, HAE may be misdiagnosed, especially in emergency settings [3]. Consequently, HAE patients may experience significant delays in diagnosis [6,7]. For patients with HAE types 1 and 2 the mean age at diagnosis is 24.5 years, and there is a mean delay of 10.4 years from the first clinical presentation until diagnosis [5,8].

Without an accurate diagnosis, HAE patients may not receive proper treatment. The consequences of inappropriate treatment are higher morbidity, unnecessary surgical interventions due to painful abdominal attacks and potential fatalities, due to upper airway edema.

A 28 year-old Caucasian woman was diagnosed with type 1 HAE in relation to her second pregnancy, about 20 years after her first disease presentations.

In early childhood she experienced abdominal pain during stressful periods and joyful events. At the age of 17 she started with oral contraceptives, which triggered severe abdominal attacks with distended abdomen, colicky pain and vomiting. The abdominal attacks started already few hours after intake of the very first pill and occurred approximately every fourteenth day. During numerous hospitalizations, she was examined thoroughly with ultrasound, CT and MR of the abdomen and she also underwent colonoscopy. All examinations were without any significant pathological findings. After some years she stopped with oral contraceptives, which resulted in a significant improvement.

During her first pregnancy in 2011 she experienced abdominal attacks from gestational week 3, approximately every fourth day. Swelling of the right arm was also seen.
at some point. The swelling was not itching and there was no associated urticaria. She has never experienced swelling of the upper airway. The vaginal delivery progressed smoothly and the postpartum period was uncomplicated. Unfortunately, she continued to experience attacks almost every second week after delivery.

In her second pregnancy in 2016, she experienced attacks with a frequency similar to the first pregnancy. During her fourth month of pregnancy she was admitted to an Emergency Department due to a swollen upper lip and facial swelling (Fig.1) and received intravenous antihistamine without any effect.

During the hospitalization the mother of the patient made an Internet search and suspected HAE as a possible cause of the symptoms. The diagnosis was discussed with the physicians, but they did not find it likely and dismissed the diagnosis without any further evaluation.

**INVESTIGATIONS If relevant**

After her discharge, she was diagnosed with HAE by her GP, who was willing to explore the diagnosis with blood testing showing C1-INH: 0.03 g/L [ref.: 0.21-0.39], functional C1-INH: 0.18 g/L [ref.: 0.7-1.3], C1q: 0.46 μmol/L [ref.: 0.24-0.61] and C4: < 0.02 g/L [ref.: 0.10-0.40]. The GP referred her to our national HAE Centre for further investigation and therapy.

Examinations made at our HAE Centre revealed a heterozygote mutation (c.152_171delinsGAG) in the SERPING1 gene which introduces a premature stop codon at position 50. The mutation is to our knowledge undescribed but is expected to cause HAE. The mutation is de novo as both parents of the patient had normal complement profiles and no SERPING1 mutation. Her first born child, who was also examined for HAE at the age of 5, also had normal complement profile and no SERPING1 mutation.

She recently gave birth to her second child, who was diagnosed with HAE at the age of 1 month based on molecular genetic analysis.

**DIFFERENTIAL DIAGNOSIS If relevant**

In 2000, a new subtype of HAE with normal C1-INH was described, which is clinically indistinguishable from HAE type 1 and 2 [9]. This new disorder was initially called hereditary angioedema type 3 and later renamed HAE with normal C1-INH activity. This condition is seen predominantly in women, especially in situations with increased levels of estrogen such as the use of oral contraceptives or during pregnancy [10]. In about 25% of these patients a mutation can be found in coagulation factor XII and recently also mutations in plasminogen and angiopoietin-1 have been detected [11,12].

**TREATMENT If relevant**

The medical treatment of HAE consists of management of acute attacks, short-term prophylaxis and long-term prophylactic therapy. Several treatment modalities have become available for management of acute HAE attacks and include plasma derived C1-INH therapy, recombinant C1-INH, Ecallantide, Icatibant and fresh frozen plasma [13].

**OUTCOME AND FOLLOW-UP**

It is psychologically and physically stressful for patients to have an undiagnosed disease. Diagnosing HAE is still a challenge which results in unacceptable diagnostic delay of many patients. In this case the diagnostic delay was ~20 years, from the first time the patient experienced an attack until the correct diagnosis was made.

An interesting point, which needs to be highlighted, is the fact that it was the mother of the patient who suspected the diagnosis after a search on the Internet. Seemingly "Doctor Google" may be a tool in the diagnostic process of a disease [8]. Unfortunately, the clinicians dismissed the correct diagnosis in the emergency setting, underlining the inadequate
knowledge about HAE, possibly due to the rarity of the disease. This emphasizes the importance of increasing awareness of this condition, which can easily be diagnosed by a biochemical analysis [14]. When HAE is suspected, laboratory analysis for C1-INH concentration and function should be performed [4]. Confirmation of the deficiency leads to the correct diagnosis and adequate treatment can be started.

Diagnostic delay is a serious issue, as adequate treatment can only be introduced, when the correct diagnosis is established [4,6]. Even in the case of a known diagnosis, the care, especially in emergency rooms, may not be optimal [15]. In emergency settings, it is not unusual to misdiagnose HAE as an allergic reaction, which results in treatment with antihistamines, adrenaline and corticosteroids without sufficient effect [5]. In such situations, the clinician must reconsider the diagnosis.

DISCUSSION

Include a very brief review of similar published cases

The main aim of this case report is to emphasize the importance of listening to patients and their relatives and being humble to “Doctor Google”. This case also illustrates the importance of considering rare differential diagnoses to common symptoms. Health care professionals should be aware of the HAE diagnosis and the necessity of referring patients to a HAE Center or to a relevant specialist, as soon as the HAE diagnosis is considered. Diagnostic delay can be reduced when awareness of HAE is increased among physicians and other health care personal, who will meet these patients in the emergency care setting.

The authors declare that there is no conflict of interest regarding the publication of this paper.

LEARNING POINTS/TAKE HOME MESSAGES

3 to 5 bullet points – this is a required field

- Listen to the patients – “Doctor Google” may be an essential tool in the diagnostic process of a rare disease.
- Sometimes, HAE is unfortunately misdiagnosed as an allergic reaction, which results in treatment with antihistamines, adrenaline and corticosteroids without sufficient effect.
- When HAE is suspected, laboratory analysis for C1-INH concentration and function should be performed.

REFERENCES

Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)


**FIGURE/VIDEO CAPTIONS** figures should NOT be embedded in this document

Figure 1: 28-year-old woman hospitalized with massive edema of the upper lip during pregnancy.

**PATIENT’S PERSPECTIVE** Optional but strongly encouraged – this has to be written by the patient or next of kin

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Date: 31.07.2018

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