

## Medical-legal aspects of Hereditary angioedema complicated with severe laryngeal attack and fatal outcome: case report

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**Abstract:** We report the case of a young boy with recurrent facial edema from his third year of life, diagnosed later with hereditary angioedema (HAE), who died of severe fatal laryngeal attack at the age of eleven. The father had milder HAE attacks until the age of 30, when he was diagnosed with systemic lupus erithematosus and the oldest brother has recurrent abdominal pain attacks, with long asymptomatic period. Family history revealed another three members who died suffocated at different ages, without any diagnosis. The death of the young boy happened in a small hospital two hours after admission, while few ineffective procedures were performed. We consider that HAE severity and fatality risk were underestimated by medical staff and the fatal outcome of HAE attack in the youngest child could have been possibly prevented in a better equipped medical unit. This case highlights the need to raise the profile of HAE within the medical community and to improve prophylaxis and treatment of this potential fatal disease.

**Key Words:** fatal outcome, hereditary angioedema, laryngeal attack.

Hereditary angioedema (HAE) is a rare disease due to inherited C1-inhibitor (C1-INH) deficiency, consisting in recurrent and unpredictable episodes of edema of the skin, upper respiratory airways and intestinal tract, usually starting in childhood or adolescence [1]. HAE diagnosis is based on family history, clinical picture and laboratory confirmation showing quantitative decrease in levels of C1-INH protein (type I) or decreased C1-INH activity (type II) [2]. Early onset of symptoms and frequent attacks in childhood predict a more severe disease in adulthood [3]. Significant variability in location and disease severity is noted, even in the same family, with some individuals carrying causative mutations, being clinically asymptomatic while others have frequent, severe attacks [4]. Some patients have symptoms limited to the gastro-intestinal tract,

complicating the recognition of the disease and leading to unnecessary surgical interventions. HAE is associated with a significant delay in diagnosis in Europe, which varies from 8 to 16 years, but more than 50 years delays have been reported [5]. The confusion with allergies is frequent, due to a similar clinical picture, leading to inadequate medical attitude in many cases and increasing the risk of death. Since HAE mechanism is not mediated by histamine, but bradikinin, the attacks do not respond to antihistamines, corticosteroids and adrenaline, which are the usual drugs used in the treatment of allergies [6]. Most European countries have national HAE registries, reference and excellence centers with trained specialists able to recognize and treat all kinds of HAE patients. The actual medical attitude in HAE patients, according to international guidelines, consists in long term and short

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term prophylaxis with new medications, mainly C1-INH concentrate and bradikinin-receptor antagonist [7].

CASE PRESENTATION

We report the case of a young boy born in 2002, who first came to an allergist consultation in 2009 for recurrent episodes of facial edema since his third year of life, considered allergic reactions, possibly to food or insect stings. The frequency of attacks was 2-3 episodes per year during four years and aggravated during the last year, leading to frequent urgent presentations to pediatric hospitals. He was treated with corticosteroids and antihistamines and no allergists consultation or investigation were performed. The diagnosys of HAE was confirmed by medical history, the clinical picture and significant low plasma levels of C1-INH and C4. The long term prophylaxis with tranexamic acid was started, with initial good response, but was associated with clinical aggravation when dose reduction was attempted. He was referred to his family doctor and pediatrician from hospital with clear documentation and diagnosis, including recommendations for medical attitude in case of severe attacks. He was also referred to the national reference center, but he did not received any other HAE prophylaxis, since it was not available. He continued to have more frequent and severe episodes of facial edema, sometimes accompanied by abdominal pain, vomiting and mild respiratory symptoms. In December 2013 he had a very severe episode of facial and laryngeal edema, for which was admitted to a small hospital situated at 60 km from the capital, with no possibility to administer adequate treatment and unfortunately he died of asfixia two hours after admission.

Resuscitation was inefficient, other therapies such as fresh frozen plasma and traheostomia were not administered. The medical-legal autopsy was performed and confirmed the death due to laryngeal edema and acute respiratory failure, in a patient with known HAE.

Family history

The history of this family diagnosed with HAE in 2009 revealed three affected members : father and the two sons and another three members of whom we had information that died suffocated at different ages.

The father of the died boy, born in 1965, was retrospectively diagnosed with HAE in 2009. His personal medical history revealed facial angioedema episodes from adolescence until 30 years and spontaneous remission of HAE after onset of SLE. The C1-INH plasma levels and C4 were constantly low, confirming the diagnosis of HAE type I. The family history revealed that his father suffered from recurrent facial edema and died of asfixia around age of 65, one sister of his father died suffocated around age of 35 and one cousin died suffocated at 40 years age. The oldest brother of the died boy, born in 1999, was asymptomatic at first presentation in 2009, except rare abdominal cramps, but he had two operations during his first year of life for presumed intestinal occlusion, not confirmed. The plasma level of C1-INH was low, with decreased activity (26%) and low C4. During adolescence he started to have more frequent attacks of abdominal pain, with increased severity and duration, but he never had facial edema or respiratory symptoms.

The delay of HAE diagnosis in this family varied from 4 years in the most severe pediatric case, to 24 years in the adult case.

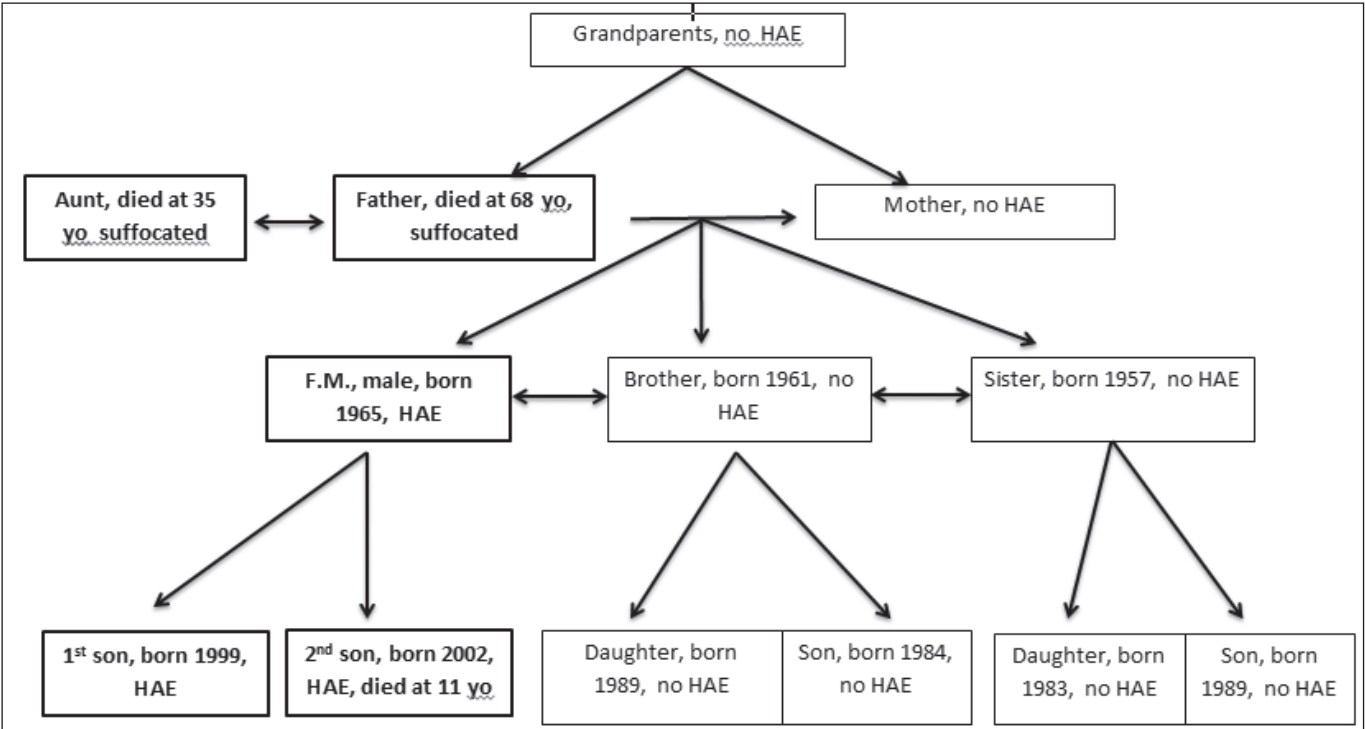


Figure 1. Genealogical tree of HAE family ( the affected members in bold).

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## DISCUSSION

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The fatality risk of HAE is well recognized, due to laryngeal attacks in most cases. Lifetime fatality rates have been estimated at between 10% and 30% and 25% of families surveyed in the European HAE register reported an HAE-related fatality, almost exclusively caused by laryngeal edema [8]. It is noted in the literature that, because the episode fatality rate of laryngeal edema is relatively low, patients may experience many such attacks which resolve spontaneously or with treatment and therefore may fail to treat laryngeal symptoms as a medical emergency. Actual treatment of HAE consists in long term and short term prophylaxis with agents such as attenuated androgens and antifibrinolytics or newer and more expensive medications, such as C1-INH concentrate and bradikinin-receptor antagonist [7]. For acute attacks, tranexamic acid is of very limited benefit and attenuated androgens are not effective [9]. Current C1-INH concentrates for intravenous administration have proven safe and effective for prophylaxis and treatment of acute attacks [10]. Another modern proven therapy of HAE attacks is icatibant, a bradikinin-receptor inhibitor for subcutaneous administration, licensed in 2008, with orphan drug status in EU, Australia and USA [11]. Fresh frozen plasma might be an effective cheaper alternative for treatment of some HAE attacks when other therapies are not available [12].

The fatal evolution of the eleven years old boy due to a HAE attack with severe laryngeal edema rises many problems regarding the medical resources needed to treat rare diseases such as this one, as well as the reported reduced awareness about HAE within medical community and patient population [13]. Despite the documented diagnosis of HAE, the treatment usually administered in pediatric hospital during attacks consisted in antihistamines and corticosteroids, like in allergic reactions. No laryngeal examination has been performed during the fatal attack.

At the moment of this tragic event, in Romania there was no pathogenic HAE medication available, which were not registered or considered too expensive by health authorities. Some patients could obtain attenuated androgens by special order from other countries and for a reasonable cost. Shortly after this HAE fatal case, a plasma-derived C1 - INH concentrate became available in one big Emergency Hospital from the capital of the country. The second important aspect impacting the HAE prognosis is the frequent confusion with allergic

angioedema and lack of consensus between all specialists involved in diagnosis and treatment of this disease [14]. Since allergic diseases are generally considered a trivial pathology and it is not included in the medical university curricula, many other specialists have low level of information about the more severe diseases, with allergic -like clinical picture, but different mechanism and management [15].

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## CONCLUSION

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We reported a case of a family with HAE, showing the different clinical pictures and evolution of three members, one of them recently dead in hospital, at age of eleven years, due to severe HAE attack with laryngeal edema. We concluded that the fatal outcome of HAE in the youngest child could have been possibly prevented, the disease severity was underestimated and the medical attitude was not adequate. Prophylaxis and treatment of this rare disease is still problematic in our country, misdiagnosis and frequent confusion with allergy may lead to delayed or inadequate medical attitude. The difficult situation of HAE patients is mainly due to reduced medical resources for diagnosis and treatment, to low level of information and education of medical staff, health authorities and general population.

There is an urgent need for more allergy and HAE regional reference centers, for improved information and education regarding HAE, for application of updated consensus regarding HAE management by all specialists and allocation of higher resources for treatment of this severe disease.

**Patient Consent for publication.** Written informed consent was obtained from the mother of the dead child for publication of this case report. A copy of the written consent is available for review by the Chief Editor of this journal.

**Conflict of interest.** The authors declare that they have no conflict of interest relating to this work and manuscript.

**Acknowledgment.** PML is the allergist who first diagnosed HAE in this family, collected the data , obtained the informed consent, drafted and approved the manuscript and choose the journal for publication. CB is the internist who diagnosed and treated the adult patient for SLE, referred him and his family to allergist, contributed to approving the final draft . Both authors read and approved the final manuscript.

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