



Letter

Delayed diagnosis of hereditary angioedema Thirty-nine years of inadequate treatment

Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is a rare disorder that is inherited as an autosomal dominant trait (approximately 75% of patients) or results from *de novo* mutations.^{1,2} In affected patients, quantitative (type I) or qualitative (type II) deficiency of functional C1-INH can cause recurrent swelling episodes in various body parts, including the upper airway, with potentially fatal consequences. Gastrointestinal attacks are excruciatingly painful and may mimic symptoms of acute abdomen. Because of the ambiguous pathologic findings and low awareness of HAE-C1-INH among physicians and the public, misdiagnoses and diagnostic delays of several years are common.^{2–6} Not only does this cause frequent hospitalizations and unwarranted medical procedures, it also is life-threatening in cases of laryngeal attacks.⁷

By reporting on a case of HAE-C1-INH in a 45-year-old woman with 39 years of misdiagnosis; inadequately treated symptoms, including gastrointestinal attacks, facial swelling, and upper airway edemas; and numerous inappropriate surgical interventions, we want to raise awareness of HAE-C1-INH, its symptoms, and the need for timely diagnosis for an optimal management of the disease.

First symptoms manifested as airway obstruction at the age of 3 years after paracentesis of the eardrum. The patient spent 2 days in intensive care, but no diagnosis could be established. During childhood, she had gastrointestinal attacks with each common cold and facial swellings after dentists' appointments.

With onset of menstruation, symptoms worsened, with attacks 1 to 2 times monthly without any obvious triggers. At the age of 12 years, after having seen various physicians because of frequent gastrointestinal pain, she was wrongly diagnosed as having appendicitis, which resulted in an unnecessary appendectomy.

At the age of 23 years, recurrent gastrointestinal attacks led to hospitalization with a diagnosis of suspected epigastric hernia and her first of 4 unnecessary repair operations. Three months later, she was again hospitalized and underwent an endoscopic retrograde cholangiopancreatography and a gastrointestinal endoscopy, revealing free peritoneal fluid, and was admitted to psychosomatic inpatient rehabilitation. At 25 years of age, suspected inguinal hernia led to repair surgery followed by Treitz hernia repair surgery 4 months later. Subsequent gastrointestinal endoscopy did not add any diagnostic information such that at the age of 27 years the

patient underwent another repair operation because of wrongly diagnosed inguinal hernia relapse. This procedure was immediately followed by a gastrointestinal attack, leading to further hospitalization with various examinations at which time pancreatic cancer was suspected. Pancreatomy revealed no tumor but triggered painful reiterating gastrointestinal attacks. Recurrent gastrointestinal pain was treated with analgesics and led to abdominal adhesiolysis at the age of 30 years. After a capsule endoscopy with negative results, another gastrointestinal endoscopy, and endoscopic retrograde cholangiopancreatography, the patient was hospitalized and an endoscopic papillotomy was performed. Between 35 and 37 years of age, she underwent her second and third abdominal adhesiolysis and magnetic resonance imaging, with negative results. Another dentist's appointment at the age of 38 years resulted in facial swelling and airway obstruction; the patient was transferred to intensive care and received high doses of antihistamines, corticosteroids, and adrenaline, without effect. Two years later, swelling of the hand raised the diagnosis of possible rheumatism. During this time, subileus and free peritoneal fluid were repeatedly diagnosed. At the age of 42 years, the patient experienced facial swelling and airway obstruction after a tooth extraction. She was transferred to intensive care, where treatment with cortisone and adrenaline remained inefficient. Eventually, she was treated with human pasteurized C1-INH concentrate, which provided rapid relief. Two months later, 39 years after first manifestation of symptoms, the diagnosis of type II HAE-C1-INH was confirmed by complement testing.

Currently, attacks of the gastrointestinal tract, face, upper airway, and extremities recur 1 to 2 times weekly. The patient has been trained on self-injection and successfully administers human C1-INH concentrate at early signs of symptoms.

Because of the ambiguity of symptoms and low physician awareness of the disease, delayed diagnosis of HAE-C1-INH is common. Mean diagnostic delays between 8 and 9 years have been estimated in international patient surveys and were even higher in nationwide surveys in Spain, Denmark, and Germany, ranging between 13 and 16 years.^{2–6} In the case reported here, time from first symptoms to diagnosis of HAE-C1-INH was exceptionally long and characterized by inadequately treated episodes of angioedematous attacks, including airway obstruction that was not recognized as a symptom of HAE-C1-INH and, at worst, could have been fatal. After a long ordeal of numerous unnecessary medical assessments and interventions, HAE-C1-INH was identified as the cause of the symptoms on successful treatment of airway obstruction with human C1-INH concentrate. The patient's father, who has occasional mild swelling attacks, was retrospectively diagnosed as having HAE-C1-INH. Review of the family history of edemas could

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therefore have indicated the hereditary origin of the symptoms at an earlier time and, through timely diagnosis, prevented the patient from unnecessary interventions. This would have facilitated appropriate treatment with C1-INH concentrate or other agents not only of painful gastrointestinal but also of potentially fatal laryngeal attacks.

On appearance of recurrent ambiguous symptoms of gastrointestinal pain, not only should a review of family history be performed but also laboratory analyses for C1-INH level and function to confirm or refute a deficiency.⁵ Decreased C1-INH and C4 levels and reduced functional C1-INH levels are predictive of HAE-C1-INH,⁸ whereas normal serum bilirubin, alkaline phosphatase, and alanine aminotransferase levels can rule out biliary obstruction and hepatitis.⁹ Computed tomography can rule out appendicitis and diverticulitis by revealing normal pericolic fat and is suggestive of HAE-C1-INH with prominent mesenteric vessels and ascites or massive small bowel or colonic edema. Less expensive ultrasonography can identify accumulated peritoneal fluid attributable to edema of the bowel wall and thus facilitate the diagnostic process.^{8–10} HAE-C1-INH is also often misdiagnosed as allergic angioedema, which is more common but, unlike HAE-C1-INH, often comes with itchy hives, is not connected with abdominal pain, and can be treated with corticosteroids and antihistamines.

This case describes a long ordeal of wrong diagnoses, inappropriate treatment, unnecessary surgical interventions, numerous days of hospitalization, and thus a considerable impairment of life quality, underlining the importance of raising physician awareness of HAE-C1-INH.

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