Hereditary angioedema restricted to the digestive tract

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Hereditary angioedema (HAE) is a rare autosomal disease. It is estimated to affect 1 in 10,000 people. Usually, it presents as recurrent attacks, which are dominated by severe subcutaneous or submucosal localised oedema, which are most likely to last for 2 to 5 days. The most frequent localisations of changes are extremities, abdomen, genitourinary track, face, skin, and upper respiratory tract. Around 20% of cases present without family history because they are *de novo* mutations [1].

A 28-year-old male presenting with nausea and vomiting with digestive and coffee ground contents and abdominal pain (mainly concentrated in the left iliac fossa) was admitted to the surgery department in August 2010. Exploratory laparotomy was performed, and no changes were found. Furthermore, upper G.I. endoscopy showed mild inflammation and oedema of the duodenal bulb.

In the following years the patient was readmitted due to similar symptoms several times a year. Family history was negative. Tumour markers levels were all the within normal rage. Subsquently the patient underwent computer tomography (CT) and 5 cm sigmoid stenosis was observed. Furthermore, colonoscopy revealed only haemorrhoids with no other pathologies. Thyroid hormones panel was performed with all results (TSH, FT3, FT4) within normal range. Lyme disease was excluded after clinical observation and negative test for antibodies to *Borrelia burgdorferi*. In December 2010 abdominal USG revealed fluid in the peritoneal cavity. Whipple disease was excluded with upper GI and duodenal biopsy histopathology and immunohistochemistry, including anti-Schiff stain. Daily excretion of porphyrin and its derivatives was measured and the results were within the normal range. Furthermore, abdominal tuberculosis (negative QuantiFERON-TB test) and iron deficiency anaemia were excluded. The next hospitalisation took place in July 2013. Vascular aetiology of the disorder was excluded following angio-CT examination and doppler USG. Due to positive hydrogen test, lactose intolerance was detected (lactase enzyme supplementation was introduced). Viral infections such as cytomegalia and toxoplasmosis were ruled out (negative IgM and IgG antibodies). Coeliac disease diagnosis was rejected (negative TTG antibodies). Repeated lowered phosphorus concentration confirmed chronic hypophosphataemia. In immunological testing lowered concentration of complement C4 was discovered. Hence, the patient was directed to the Immunology Clinic where the testing was extended: C3, C4, and inhibitor C1 esterase were measured and the results were, respectively: 1.21 g/l (normal), 0.006 g/l (lowered), and 0.04 g/l (lowered) with lowered activity of C1 inhibitor (35.8%). Final diagnosis of hereditary angioedema type 1 was established in September 2013.

Since the final diagnosis the patient has been treated with C1 inhibitor concentrate or recombinant human C1-INH (rhC1-INH) at the time of attack. Recently, the dose of C1 inhibitor concentrate had to be increased due to progression of symptoms. Response to this treatment is positive with slight hypotension episodes, which normalise following fluid administration.

Only a few cases of HAE with abdominally restricted symptoms have been described. However, symptom presentation was different from our case in many key aspects. The undeniable problem with HAE diagnosis was stressed by Zanichelli *et al.* [2], who showed that 185 of 418 patients suffering from the disease are misdiagnosed one or more times during their observation. Misdiagnosis risk factors were: older age at the disease onset and lack of positive family history. In some described cases, it has been shown that family members, even those not diagnosed with HAE, had a history of

various oedemas [3, 4]. A 50-year-old woman with only abdominal pain was diagnosed 20 years after the onset of symptoms. Her father and sister had similar symptoms and skin oedema [3]. Another case describes a 44-year-old woman with features of colitis, and her family history was also positive [4]. Abdominal symptoms are present in up to 93% of patients suffering from HAE [5]. However, extremely rare symptoms are restricted to abdominal symptoms only, as in our case. The majority of patients, in addition to abdominal pain, present skin changes, approximately 50% – upper respiratory tract symptoms [5], and 95% – oedema of extremities [6]. Locascio *et al.* [7] described the case of a 34-year-old women with abdominal pain and history of oedema in extremities and face, which was highly suggestive of HAE. Typical attacks of HAE symptoms increases in severity during 48 h, but decrease thereafter. Maximal time of a single disease episode is estimated at 5 days [8]. It was not the case with the current patient, as the frequency and severity of attacks increased constantly. In this case, the patient's recent attack lasted 10 days, 3 years after diagnosis.

In addition, there have been other similar cases of HAE. However, the origin of symptoms turned out to be the large intestine. There were similar symptoms observed in family members. Colonoscopy examination indicated swelling, inflammatory changes in the large intestine (extensive acute colitis, mucosal edema of the colon, severe cramps of intestine) [4]. In our case, no changes in colonoscopy were revealed, and only mild inflammatory duodenal bulb lesions could be observed.

In conclusion, HAE with only gastrointestinal symptoms is rare and may be the cause of diagnostic problems. Family history is not always revealed. This report demonstrates the importance of consideration of HAE restricted to one system, namely only to the digestive tract. It may play a crucial role in shortening of the diagnostic process and introducing the targeted treatment.

Conflict of interest

The authors declare no conflict of interest.

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