Case Report

Hereditary angioedema and gastrointestinal complications: Case report

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Abstract

Background: Hereditary angioedema (HAE) caused by C1-esterase inhibitor(C1-INH) deficiency is an autosomal dominant disease resulting from mutation in the C1-inhibitor gene. In classic HAE, abdominal attacks are mostly characterized by pain, vomiting and diarrhea. **Case presentation:** A 34 year old female presented with a 12 years history of episodic severe cramping abdominal pain, associated with vomiting and diarrhea. Each episode lasted for a few days and would resolve spontaneously. All the laboratory investigations performed during the episodes were normal except C4 level (< 8 mg/dl) and C 1 esterase inhibitor functional activity (5%) and normal C1 inhibitor level (0.41 G/L) supporting diagnosis type II HAE. **Discussion:** Hereditary angioedema is a rare genetic disorder. Gastrointestinal tract involvement is an important feature and one of the most common in HAE. Patients suspected of having angioedema should be screened by measuring C4 levels which are typically low except between episodic phases. If the C4 level is decreased, antigenic and functional levels of C1-INH should be measured to confirm the diagnosis. **Conclusion:** In summary, the diagnosis of angioedema should be considered in any patient with recurrent abdominal pain of obscure origin. There may not be any abnormal findings between attacks, therefore a comprehensive history and physical examination is of utmost importance

Key Word: HAE, C1 INH, Angioedema, C4 level

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INTRODUCTION

Hereditary angioedema (HAE) caused by C1-esterase inhibitor (C1-INH) deficiency is an autosomal dominant disease resulting from mutation in the C1-inhibitor gene[1] and it can be associated with quantitative (type I) or qualitative (type II) deficiency of C1-INH[2]. HAE is a rare and potentially life-threatening disease, characterized by non-pitting, non-pruritic swelling of subcutaneous tissue or submucosal tissue of the skin, extremities, respiratory and gastrointestinal tracts[3]. Involvement of the upper respiratory tract, may lead to asphyxiation which is the primary cause of death among HAE patients[4]. The age of onset of HAE is variable and can present in children less than one year old, with laryngeal attacks developing usually after the age of three and increasing in frequency after puberty[5]. In classic HAE, abdominal attacks are mostly characterized by pain, vomiting and diarrhea but rarely occur in the absence of other clinical features. These symptoms are due to transient edema of bowel wall, which can lead to intestinal obstruction, ascites and hemoconcentration[6]. Thus abdominal HAE attacks contribute significantly to the reduced quality of life and economic burden of HAE patients, moreover the accurate diagnosis of the disease, especially in patients who present only with recurrent abdominal symptoms, remains a challenge[7]. We describe a case of type II HAE in a young women presenting with recurrent abdominal pain associated with edema of small bowel wall and ascites without any other clinical features of HAE.

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CASE PRESENTATION

A 34 year old female presented with a 12 years history of episodic severe cramping abdominal pain, associated with vomiting and diarrhea. Each episode lasted for a few days and would resolve spontaneously. The patient's medical history included treatment for infertility and family history of similar episodes in her elder brother but symptoms are in milder form and less frequently. During her first episode in 2005, USG showed multiple sluggishly peristaltic dilated small bowel loops noted predominantly in upper left quadrant of abdomen with inter bowel free fluid and minimal free fluid in Morrison's pouch (?subacute intestinal obstruction). After conservative management symptoms were subsided and again patient was presented with similar signs and symptoms frequently and admitted in casualty for conservative management. In 2007, she was investigated for infertility and all investigations were normal. Then she was on hormone therapy which aggravated her symptoms and frequency of abdominal pain. A year later patient presented with similar complaints, USG and CT scan showed mild to moderate free fluid in abdomen, enlarged ovaries with bilateral PCOD and edematous small bowel wall thickening S/o peritonitis. During laparoscopic examination, small tubercles were seen on right fallopian tube and anterior abdominal wall. Routine fluid examination showed raised proteins (4.74), total cell count 300 with lymphocytes predominance. ADA, TB PCR negative and histopatholgy of tubercle was nonsignificant. Started on antituberculous drug for six months and similar episodes occurred even during treatment. Seven years later patient presented similar episodes in severe form. USG showed thickening of small bowel wall at 15 cm from duodenal junction involving approximately 15 cm bowel with stricture proximally which was not decreased even after conservative management. Surgical resection and anastomosis was done after removing 15 cm bowel segment. Histopathology report was not conclusive for diagnosis. Even after surgery, patient was having similar episodes with small bowel sometimes large bowel wall thickening and free fluid in abdomen. We gave our patient an extensive evaluation, which included several times endoscopy and colonoscopy over the span of 12 years with normal findings. Computed tomography (CT) of the abdomen performed when the patient was asymptomatic showed a normal small bowel wall. Also all the laboratory investigations performed during the episodes were normal except C4 level (< 8 mg/dl) and C 1 esterase inhibitor functional activity (5%) and normal C1 inhibitor level (0.41 G/L) supporting diagnosis type II hereditary angioedema. Our patient's symptoms improve with anti-inflammatory and analgesic drugs and supportive treatment.

DISCUSSION

Hereditary angioedema is a rare genetic disorder and the incidence in India has not been established as yet[8]. In 1888, Osler documented its hereditary nature, which was further defined as autosomal dominant by Crowder and Crowder in 1917[6]. No gender or ethnic group differences have been noted. Symptoms typically worsen after puberty[6]. Diagnosis of HAE in patients with recurrent abdominal pain can be challenging, especially in the approximately 50% of cases that present only with abdominal symptoms[7] and on average it takes 10 years from the time of onset of symptoms until a diagnosis is made[9]. Historical data suggest that up to 80% of HAE patients have recurrent abdominal pain[10]. HAE is divided in to 3 types: (1) HAE-I is caused by a C1-INH gene mutation resulting in a low level or absence of antigenic and functional C1-INH; (2) HAE-II, caused by a C1-INH gene mutation resulting in a normal or high C1-INH level indicating functional impairment; (3) Estrogen dependent HAE, which has normal C1-INH levels and function and normal genetic analysis, but a direct correlation with estrogen levels[6]. The inciting factors for HAE includes physical injury, medical or dental procedure, psychological stress, menstruation, infections or certain medications such as exogenous estrogen and angiotensin-converting enzyme inhibitors[11]. As estrogen increases disease severity, women tend to have more severe disease than men. The severity of presenting symptoms varies widely, even among family members[8].The angioedema in HAE develops secondary to excess bradykinin production due to low levels of functionally active C1 esterase inhibitor. This leads to the activation of the kallikrein-kinin system causing the release of vasoactive peptides[12]. C1-INH inhibits the formation of activated C1 and cleavage of C2 and C4 and also to generate bradykinin from C2[6]. Gastrointestinal tract involvement is an important feature and one of the most common in HAE. The difficulty in recognizing gastrointestinal symptoms as being related to HAE often leads to delay in diagnosis and unnecessary surgery[5]. The abdominal pain can present acutely or as recurrent pain and is described by patients to be cramping and colicky in nature[13].Typical observations associated with abdominal angioedema include small bowel mucosal thickening, thumb printing of bowel wall and ascites[14]. Severe consequences such as circulatory collapse may occur due to a combination of vasodilatation, fluid loss from emesis and diarrhea, and fluid extravasations from bowel wall edema and ascites[5]. Prior abdominal surgeries further complicate abdominal attacks due to the possibility of adhesions causing small bowel obstruction. The majority of abdominal attacks last 2-4 days with preceding symptoms of irritability, fatigue, hunger, aggressiveness and erythema marginatum.[15] The

diagnosis of angioedema is made in the context of the appropriate constellation of medical history including family history and clinical findings along with supportive laboratory data. HAE should be suspected when there is history of recurrent angioedema without urticaria and an early age of onset. Symptoms typically worsen over 24 hours and subside in 48-72 hours. Patients suspected of having angioedema should be screened by measuring C4 levels which are typically low except between episodic phases[6]. The C4 test is inexpensive, common to most hospital laboratories and typically has high sensitivity and specificity, with at least 95% of patients showing a reduced C4 level during remission and virtually 100% showing reduced C4 during an attack. If the C4 level is decreased, antigenic and functional levels of C1-INH should be measured to confirm the diagnosis[16]. It is not recommended to measure complement C3 and CH50 levels, as they are near normal in angioedema[6]. There are three therapeutic goals for patients with angioedema: immediate treatment, short-term and long-term prophylaxis. In acute emergencies such as laryngeal edema, the immediate treatment is to maintain an open airway. Abdominal pain secondary to edema can be controlled with analgesics. Corticosteroids are of little benefit for patients with angioedema. Short term prophylaxis involves the withdrawal of precipitating factors such as oral contraceptives or hormone therapy as angioedema can worsen with estrogen therapy. Attacks have also been associated with stress. The use of fresh frozen plasma remains controversial as it might provide factors that could worsen the angioedema. Replacement of the missing enzyme as C1-INH concentrate is the ideal therapy as an immediate, short term or long term treatment[6]. C1 estarase inhibitor concentrate is available in western countries where it has become the therapy of choice for life threatening attacks[17]. But the use of C1 esterase inhibitor (Human) products is associated with serious arterial and venous thromboembolic events[7]. Recent evidence showing that bradykinin is the main mediator of HAE causing vasodilatation and permeability of vessels has led to development of novel agent which either inhibits bradykinin or blocks its receptors. First agent ecallantide which is kallikrein inhibitor has recently been approved for acute management. Another drug icatibant which is bradykinin receptor antagonist has been approved for use in European Union but is still under trial in United States[18]. Prophylaxis is recommended for those patients who experience recurrent episodes of laryngeal edema[4]. Danazol, an attenuated androgen is used for both short and long term prophylaxis[6]. The duration of prophylactic treatment usually depends on the severity of disease and toxicities associated with it, which includes weight gain, dyslipidemia, abnormal liver function test, hepatic cyst and hepatic carcinoma[19]. It cannot be given during pregnancy due its musculanization effect on the fetus and also in children due to its effect on closure of epiphyses.

The physician should be aware of the disease as its presentation may mimic anaphylactic reaction and critical time may be wasted in treating it for same. It is also important to educate patients regarding avoidance of triggering factors and early reporting to the hospitals if the symptoms develop. Twenty percent of the HAE patients with HAE develop autoimmune diseases later in life which includes chronic urticaria, gloerulonephritis, thyroiditis, inflammatory bowel disease, pancreatitis, systemic lupus erythematous and juvelnile arthritis[8]. A recent study found that mortality was 29% in patients with undiagnosed HAE as compared to 3% in patients with known diagnosis of HAE[5]. This stresses the importance of early diagnosis and patient education and access to treatment can greatly reduce mortality.

CONCLUSION

In summary, the diagnosis of angioedema should be considered in any patient with recurrent abdominal pain of obscure origin. There may not be any abnormal findings between attacks, therefore a comprehensive history and physical examination is of utmost importance. Confirmatory laboratory data should be obtained and imaging studies performed to confirm the diagnosis. A combination of an individualized action plan, pharmacologic therapy and prophylactic measures can help prevent years of patient distress and unnecessary surgeries and decrease mortality.

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