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Case Report

Severe Abdominal HAE Attacks: An Analysis of 7 Cases

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Abstract

Abdominal angioedema attacks are a frequent and typical symptom of hereditary angioedema (HAE) but very often generate diagnostic problems. The study presents laboratory and clinical findings of 7 patients with HAE 1/2 hospitalized due to severe attacks. In all cases, at admittance severe abdominal pain, flatulence, strong weakness, different grade of nausea/vomiting or diarrhoea and abundant free fluid in peritoneal cavity were present. In the history of all patients, recurrent 2 to 3 day long abdominal attack with ascites, were announced. Laboratory data done before the treatment showed elevated leukocytosis, hematocrit, serum glucose, high D-dimers and decreased value of APTT. All patients had an abdominal ultrasound examination, in 5 patients additional abdominal angio-CT was performed to exclude thromboembolic episode. The infusion of human C1 inhibitor concentrate was administered as causative treatment. Completely withdrawal of symptoms was noted up to72 hrs after infusion. In addition all laboratory parameters normalized as well as the free fluid in abdominal cavity disappeared, however, D-dimers serum level despite a decreasing tendency reached the normal range just after 2 weeks.

Keywords: C1 inhibitor; Abdominal attack; Hereditary angioedema; Ascites, D-dimers

1. Introduction

Hereditary angioedema (HAE) is one of bradykinin dependent edema. Is inherited in an autosomal dominant manner. It is caused by one of more than 450 different mutations in SERPING1 gene, which codes C1 inhibitor (C1-INH). The new mutations in first patient's generation are responsible for the diseases in approximately 20-25% of cases. There are two types of HAE. The first type (HAE 1) is associated with the lack of C1-INH protein and the second type (HAE 2) with decreased activity of C1-INH. The estimated disease incidence is 1 in 50,000 individuals

and varies depending on the region [1-3]. During the course of both types of HAE, the attacks of angioedema are localized in the skin or mucous of the respiratory and gastrointestinal tract [4, 5]. The bradykinin angioedema attack differs from other swellings, including the most common histamine- dependent swelling, in longer duration, slower build-up phase, lack of urticaria, lack of pruritus and presence of prodromal symptoms [3]. Abdominal attacks are one of the most common forms of HAE. Intestine oedema leads to partial or complete bowel obstruction. Abdominal attack symptoms are pain, nausea, vomiting and diarrhoea. It might lead to hypovolaemia and shock. Both abdominal and laryngeal attacks are life-threatening conditions. In the past, surgical treatment of HAE abdominal attacks was the most common mistake as a result of lack of, or wrong differential diagnosis [4, 5]. The typical edema treatment, like anti- histamine drugs, systemic steroids or adrenaline in bradykinin dependent edema, is ineffective. It requires administration of human or recombinant C1-INH, a bradykinin receptor blocker or a kallikrein inhibitor. Late drug administration affects the slower regression of symptoms and may complicate the differential diagnosis of other causes of acute abdominal pain [3]. Physicians at the emergency units may face these problems. The aim of the study was the retrospective analysis of patients with HAE abdominal attacks who were hospitalized due to the severity of the attacks.

2. Materials and Methods

Seven adult patients (5 women & 2 men between the age of 18 to 57 years) with C1-INH HAE type 1/2, diagnosed and treated in our outpatient HAE Center, were enrolled in the study. They fulfilled the criteria of prolonged hospitalization over 24 hours due to very severe abdominal attacks. Their clinical characteristic are summarized in Table 1. Family history was positive in 4 patients. The mean age of the first onset of angioedema was 8.7 yrs (3-15 yrs). In all patients case history revealed the presence of 2 to 4 days long abdominal attacks followed by efficient treatment with the infusion of C1-INH concentrate. In 4 cases, abdominal symptoms were connected with recurrent ascites, disappearing together with the abdominal symptoms. In 2 patients (no 2 & 6) abdominal attacks were the only symptom of the disease. The diagnosis of C1-INH HAE type 1 or 2 was based on; case and family history, and an estimation of antigenic C1-INH C4 level as well as functional C1-INH. The C1-INH and C4 serum levels were determined during remission using the nephelometric metod on Behring Nephelometr 100 analizator. Activity of C1 inhibitor (fC1-INH) was measured with the colorimetric kinetic method using a chromogen substract (Berichrom C1 Inhibitor &Komplement Reagents - DADE Behring) on Behring Coagulation Timer analyser.

Medical history from local emergency units was analysed. At admission, the general state of patients was very serious because of the abdominal pain, weakness and flatulence, diarrhea or vomiting. In 3 patients, besides severe abdominal symptoms, peripheral angioedema was present. Clinical symptoms were evaluated from the medical history using the popular symptom score (no symptoms, mild, moderate and severe) with a scale of 0 to 3. Laboratory tests of white blood cells (WBC), hematocrit (Hct), C-reactive protein (CRP), serum glucose level, APTT and D-dimers serum level was determined and abdominal ultrasonography (abdominal USG) was conducted. All clinical symptoms, laboratory and ultrasonography were analysed twice; at admission and after the 72 hours.

Five cases (case no 1-5) required angiography computed tomography (A-CT), at admission, in order to exclude thrombosis in visceral vessels.

No	sex	Age at the time of hospitalization	aC1-INH*	fC1-INH**	C4***	HAE type	Family history	Age (years) / location of first HAE attack	Main and additional HAE attack location
1.	F	57	0.09	30.6	0.016	1	positive	15 - hand	abdomen, arm
2.	M	32	0.06	35.8	0.09	1	positive	10 - abdomen	abdomen
3.	F	30	0.37	19	0.02	2	negative	10 - face	abdomen
4.	F	25	0.05	9.3	0.049	1	negative	3 - hand	abdomen, hand, face
5.	F	51	0.03	18.6	0	1	positive	10 - abdomen	abdomen, face
6.	M	18	0.12	45	0.1	1	positive	5 - abdomen	abdomen
7.	F	34	0.08	34	0.05	1	positive	8 - abdomen	abdomen

*aC1-INH: C1-INH antigen - normal range 0.2-0.39 g/L, **fC1-INH: C1-INH functional normal range 70-130%, ***C4: normal range 0.1-0.4 g/L

Table 1: Clinical and biochemical characteristic of the patients.

No	Leukocytosis *>**	Htc *>**	CRP mg/L * >**	D-dimers *>**	APTT - s *>**	Serum glucose mg% *>**	Abdominal USG *>**	Symptoms score *>**	Angio CT
1	18 300 > 4 100	54.8 >36.1	2.9 > 3.5	8 457 > 1 527	25.2> 26	134 > 74	+ > 0	3 > 0	Neg.
2	12 780 > 5 460	48>47,5	8.2 > 1.0	6 630 > 2 860 270***	24.2 > 24	146 > 78	+ > 0	3 > 0	Neg.
3	19 300 > 4 970	47,4>36,4	30.1>1.7	13370 > 1 538 207***	23.5 >24	127 > 80	+>trace	3 > 1	Neg.
4	10 800 > 7 300	40,5>33,6	8.1 > 1.7	34000 > 2 389 550***	22 > 25	120 > 85	+>trace	3 > 1	Neg.
5	8 510 >5 700	39.2 >34,7	3.5 > 3.2	16000 > 955 507***	22 > 26	137 > 90	+ > 0	3 > 0	Neg.
6	21 820>12 800 5790 ***	52.4> 42	170> 66 3.06 ***	5990>1 230 250 ***	30.5>31.5	108> 97,2	+ >trace	3>0	n.d.
7	17 500> 6 300	56.5> 41,5	18.2> 3,45	nd	29.7> 32	118,7> 85	+> 0	3>0	n.d.
	N: 4-10 000 uL	N: 35-45 %	N <5.0 mg/l	N <500 ug/ml	N: 26-32 Sec.	N:70-99 mg%	Abundant fluid in peritoneal cavity	0-no symtoms, 1-milde, 2-moderate, 3-severe.	Presence of trombo-embolism

*: at admission, **: after 72 hrs, *** 2 weeks later, nd – not done, N- norm

Table 2: Laboratory parameters symptoms score and treatment at the beginning of admission to the hospital and after 72 hrs. of hospitalization.

3. Results

Results of the study are presented in Table 2. In all 7 patients at admission a high symptoms' score of 3 was noted because of severe abdominal pain, strong flatulence, weakness, diarrhea or vomiting. In cases no 1, 2, 3, 6 and 7 strong weakness was observed with hypotension. In 3 cases (no 1,4 and 5) additional attacks of peripheral skin angioedema (face, arm, hand) were present. The image of abdominal cavity and small pelvis ultrasonography revealed the presence of significant amounts of intra-abdominal fluid and 4 cases exhibited regional bowel edema. In all cases, at admission, high leukocytosis, hematocrit and elevated glucose serum levels were noted as well as very high D-dimers serum level. In 5 cases (no 2,3,4, 6 & 7) CRP was elevated (in case no 6 the increase of CRP was extremely high). In cases 1 through 5 the value of APTT was somewhat decreased.

All patients received infusion of C1-INH concentrate at the hospital. In 5 cases (no 1-3 & 6 and 7) additional infusion of fluid was necessary because of dehydration symptoms and decreasing blood pressure. In all cases, time from the onset of symptoms was no longer than 4 hours. Symptoms which patients had at the time of attack gradually diminished after the infusion, but complete resolution was observed not sooner than at the 72 hour control exam. In addition, the 72 hour control exam revealed leucocytosis, Htc and serum glucose levels which returned to norm. Initial elevated CRP levels noted in cases no 2,3,4 and 7 also normalized. Only in case no 6, with extremely severe symptoms, pain localized in the appendix region, and the highest value of CRP at admission, the CRP decreased to 66 mg/l despite the disappearance of all abdominal symptoms. The complete normalization of this parameter in this patient was noted two weeks later without any additional medical intervention. Very high D-dimers serum level were revealed in 6 patients at admission and remained high. Their level normalized at the control exam performed 2 weeks later (Table 2). In 5 cases the slightly decreased APTT values returned to norm. In all patients, abdominal ultrasonography at admission revealed the presence of abundant fluid in the peritoneal cavity. No fluid in 4 cases and trace amounts in 3 cases were revelled after 72 hours.

In 5 cases (1-5) the angio-CT examination was done to exclude thromboembolic changes in visceral vessels due to severe clinical symptoms, high D-dimers, and slow regression. The result was negative.

4. Discussion

The current recommendation is that attacks are treated as early as possible. Early treatment is associated with shorter time to resolution of symptoms and shorter total attack duration regardless of attack severity and localization. All patients with HAE -1&2 should be considered for at-home therapy and self-administration training [3]. In our group of patients, late drug administration in hospital was probably one of the reasons of severity and prolonged duration of attacks. Despite adequate treatment, the course of the attacks may be more severe. It often requires hospitalization, additional test and examinations [5-7].

A severe course of abdominal attack is a result of pain and vasodilation, massive fluid extravasation with edema of the bowel wall. Ascites, as well as the fluid loss due to vomiting and diarrhea, may lead to considerable hypovolemia and hemoconcentration. When this process occurs rapidly, is responsible for the clinical circulatory

symptoms ranging from light headedness to shock of variable severity. Bork and all showed that a circulatory collapse occurred in 4.4% of all attacks. Dehydration was the explanation for high: leucocytosis, Htc and glucose in patients no 1,2,3, 6,7 [5].

CRP values in 4 cases (no 2,3,4 and 7) were significantly elevated and returned to the norm with disappearance of the symptoms. A Japanese study by Ohasawa et al. concluded that the CRP values during the course of the HAE attack should remain normal [8]. In their opinion CRP is one of the parameters that facilitate differential diagnosis with other acute abdomen reasons. Hofman et al. showed different results CRP levels were elevated in a substantial proportion of asymptomatic HAE patients and increase significantly during an abdominal attack. The possible explanation is low-grade systemic inflammatory reactions – cytokine mediated CRP liver production- in HAE patients as well as a triggering event for attacks that starts prior to symptom onset [9].

High level of D-dimers and decreased value of APTT was observed at the admission to hospital in 6 and 5 patients respectively. These observations confirm the study results of Reshef et al. [10], indicating that elevated D-dimer level is often associated with the initial phase of acute submucosal/abdominal attack of HAE normalizing gradually together with withdrawal of symptoms. In HAE patients the absence of normal inhibition by C1-INH increased fibrinolytic activity during attacks and even in remissions [11-17]. Shortened APTT is a consequence of the C1-INH deficiency and a sign of the latent activation of the kallikrein-kinin system and the intrinsic clotting system [18]. Inflammation and an acute phase reaction may result in APTT decrease. In clinical practice, elevated plasma D-dimers are considered biomarkers of extensive thrombosis but are also elevated in certain nonpathologic conditions [19]. Despite evidence of extensive activation of both coagulation–contact and fibrinolytic systems, relatively low rates of spontaneous thromboembolic events have been reported in patients with C1-INH HAE [10]. In our group of patients with elevated CRP and D-dimers together with severe course of attacks needed additional examinations (USG, angio-CT) to exclude thromboembolic events and inflammations. Typical imaging examinations findings confirming abdominal HAE attacks are thickened bowel wall and ascites [20-23]. CT and angio-CT is the most exact, but not always available imaging modality confirming the abdominal HAE attack and excluding thromboembolic events [24, 25]. In recurrent and frequent abdominal attacks ultrasound may be able to reduce cumulative ionizing radiation exposure from repeated CT. Ultrasounds allow for rapid assessment of patients, with HAE, who complain about abdominal pain and can also be useful in excluding other diagnoses such as appendicitis, ectopic pregnancy, and biliary disease [20-23].

5. Conclusions

1. HAE abdominal attacks despite casual treatment, can be severe and requiring hospitalization.
2. There are findings both in laboratory tests and USG examination confirming dehydration and displacement of fluids during an attack.
3. Imaging tests (USG, CT) confirm the abdominal HAE attack. Elevated CRP and D-dimers are very often present, but there is no specific laboratory test for the HAE abdominal attack. All possible tests should be performed to exclude other diagnosis in patients with severe abdominal HAE attacks.

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Conflict of Interest

The authors have declared no conflict of interest.

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