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Collegium Medicum

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Abdominal attacks in patients with hereditary angioedema due to deficiency of C1 inhibitor (rare disease). Diagnostic possibilities of imaging tests.

Napady brzuszne u chorych z wrodzonym obrzękiem naczynioruchowym
na tle niedoboru inhibitora C1 (choroba rzadka).
Możliwości diagnostyczne badań obrazowych.

Praca doktorska

Promotor: prof. dr hab. n. med. Tadeusz J. Popiela

Pracę wykonano w *Zakładzie Diagnostyki Obrazowej*
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Wykaz skrótów:

HAE - Hereditary angioedema

C1- INH - C1 inhibitor

CT- tomografia komputerowa

MR - rezonans magnetyczny

USG - badanie ultrasonograficzne

BK - bradykinina

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Abdominal and pelvic imaging in the diagnosis of acute abdominal attacks in patients with hereditary angioedema due to C1-inhibitor deficiency

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III

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Severe Abdominal HAE Attacks: An Analysis of 7 Cases

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Ewa Czarnobilska; Krystyna Obtułowicz

Inne publikacje na temat C1 – INH-HAE nie włączone do rozprawy doktorskiej:

1. Aldona Juchacz, Piotr Obtułowicz, Małgorzata Hendzel, Krystyna Obtułowicz.
   Tytuł oryginału: Abdominal attacs in hereditary angioedema due to C1 INH deficiency Diagnostic difficulties. Case report.
   Czasopismo: Alergologia i Immunologia Szczegóły: 2016 : T. 13, nr 3-4, s. 43-46,

2. Piotr Obtułowicz, Andrzej Urbanik, Krystyna Obtułowicz.
   Tytuł oryginału: Nawracające bóle brzucha i wodobrzusze u pacjentów z wrodzonym obrzękiem naczynioruchowym na tle niedoboru C1 inhibitora. Analiza retrospektywna.
   Czasopismo: Przegląd Lekarski Szczegóły: 2013 : T. 70, nr 5, s. 299-302,

3. Piotr Obtułowicz, Krystyna Obtułowicz.
   Tytuł oryginału: USG jamy brzusznej w diagnostyce ostrych objawów brzusznych u chorych
   z wrodzonym obrzękiem naczynioruchowym (Hereditary Angioedema - HAE).
   Czasopismo: Alergologia i Immunologia
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4. Grzegorz Porębski, Barbara Bilo, Krystyna Obtułowicz, Piotr Obtułowicz, Jan Nuijens.
   Tytuł oryginału: Rekombinowany C1-inhibitor jest skuteczny w leczeniu ostrych napadów wrodzonego obrzęku naczynioruchowego - opis przypadków.
   Czasopismo: Przegląd Lekarski
   Szczegóły: 2005 : T. 62, nr 5, s. 317-320

5. Krystyna Obtułowicz, Piotr Obtułowicz, Maria Kapusta.
   Tytuł oryginału: Wrodzony obrzęk naczynioruchowy u osób z niedoborem C1 inhibitora - rejestr krakowski.Tytuł angielski: Hereditary angioedema (HAE) in patients with C1 inhibitor deficiency - Cracow register.
   Czasopismo: Postępy Dermatologii i Alergologii
   Szczegóły: 2005 : T. 22, z. 1, s. 23-28

Spis Treści

Wstęp:

Wrodzony obrzęk naczynioruchowy na tle niedoboru C1 inhibitora (Hereditary angioedema due to C1 inhibitor deficiency – C1-INH-HAE) jest rzadkim dziedziczonym dominująco schorzeniem, o częstości występowania 1:50 000 osób. Przyczyną jego objawów są heterogenne mutacje w genie C1 inhibitora (SERPING 1), których skutkiem jest istotne osłabienie aktywności C1 inhibitora (<50% normy), głównego czynnika hamującego układ kinin ustrojowych. Następstwem tego jest skłonność ustroju do łatwego uwalniania kinin, a zwłaszcza bradykininy, następujących pod wpływem różnych bodźców lokalnych czy ogólnoustrojowych zaburzających homeostazę tkanek.

Wzrost poziomu bradykininy jest głównym powodem obrzęku naczynioruchowego u osób z wrodzonym obrzękiem naczynioruchowym. Choroba występuje pod postacią dwóch wariantów fenotypowych określanych jako typ I i II. Typ I dotyczy ponad 80% przypadków chorych z tym schorzeniem i charakteryzuje go niska masa C1 inhibitora i niska jego aktywność (<50% normy). U ok. 20% chorych występuje typ II w którym masa C1 inhibitora jest w normie lub podwyższona i jedynie aktywność C1 inhibitora jest <50% normy. Przebieg kliniczny choroby i skuteczność leków jest w obu typach podobna.

Wrodzony obrzęk naczynioruchowy na tle niedoboru C1 inhibitora charakteryzuje się kilkudniowymi napadami samoograniczającego się obrzęku naczynioruchowego tkanki podskórnej pod postacią obrzęków zewnętrznych (najczęściej dłoni, stóp, twarzy) lub tkanki podśluzowej narządów wewnętrznych (zwykle przewodu pokarmowego lub górnych dróg oddechowych).

Bradykininowy obrzęk naczynioruchowy z jakim mamy do czynienia u chorych z wrodzonym niedoborem C1 inhibitora ma swe charakterystyczne cechy różnicujące go od obrzęku indukowanego histaminą. Napady obrzęku naczynioruchowego są nieregularne, trudne do przewidzenia, narastają powoli, występuje nieregularnie, ze zmienną lokalizacją.

Charakterystycznie ustępuje samoistnie po 2-3 dniach. Nie towarzyszy mu świąd ani bąble pokrzywkowe. Jest oporny na leczenie glikokortykoidami, lekami przeciw-histaminowymi czy też adrenaliną. Do czynników prowokujących należą stres, uraz, infekcje, obfity posiłek lub głodzenie, forsowny wysiłek oraz niektóre pokarmy. Może być groźny w przypadku zajęcia narządów wewnętrznych, zwłaszcza w napadach obejmujących drogi oddechowe (mogąc prowadzić do ich niedrożności), lub napadu obrzęku w przewodzie pokarmowym, gdzie obraz kliniczny ostrych objawów brzusznych często imituje obraz ostrego brzucha i każdorazowo stanowią problem diagnostyczny oraz kliniczny. Objawy kliniczne w ostrym napadzie brzusznym każdorazowo mogą mieć inny przebieg i różne nasilenie począwszy od niewielkiego niespecyficznego dyskomfortu skończywszy na wstrząsie hipowolemicznym związanym z masywnym przesiękiem płynu do jam ciała i do światła przewodu pokarmowego czy tkanek miękkich oraz do niejasnego obrazu chirurgicznego brzucha z imitacją występowania cech niedrożności przewodu pokarmowego czy innych chorób imitujących ostry brzuch.

Cele pracy:

Celem wykonanych badań była:

1. retrospektywna analiza problemów diagnostycznych i leczniczych napadów brzusznych u 274 chorych (dorosłych i dzieci) z wrodzonym obrzękiem naczynioruchowym w przebiegu niedoboru C1-INH typu I i II.

2. ustalenie przydatności badań obrazowych (USG/CT) jamy brzusznej i miednicy w rozwiązywaniu problemów diagnostycznych napadów brzusznych u chorych z wrodzonym obrzękiem naczynioruchowym na tle niedoboru C1 inhibitora – (Hereditary angioedema due to C1inhibitor deficiency).

3. ocena przydatności badań obrazowych badań w monitorowaniu skuteczności leczenia napadu brzusznego u chorych z tym schorzeniem

4. ustalenie wartości pomocniczej roli w interpretacji zmian stwierdzanych w badaniach obrazowy jamy brzusznej w łączności z wywiadem i z badaniem fizykalnym w rozpoznaniu przyczyn napadowych dolegliwości brzusznych u pacjentów z HAE.

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BRADYKININ MEDIATED GASTROINTESTINAL EDEMA AS A CAUSE OF ABDOMINAL ATTACKS IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare hereditary disease characterized by recurrent subcutaneous or submucosal angioedema due to uncontrolled bradykinin production caused by C1-INH dysfunction. Submucosal gastrointestinal swellings provoking abdominal attacks are common and mimic acute abdomen, thus constituting a diagnostic challenge. We aimed to investigate the difficulties in diagnosing abdominal attacks in patients with C1-INH-HAE and to assess the diagnostic value of medical history, the course of the attack, abdominal imaging, and treatment efficacy. The retrospective analysis of diagnostic problems and treatment complications of abdominal attacks in 274 patients with C1-INH-HAE were performed. The value of history, laboratory findings, prodromal symptoms and course of attacks and imaging were assessed. Abdominal attacks were confirmed in 274 of the 322 patients (85%; 190 women and 84 men; age, 4–70 years). In 49% of cases, the abdominal attack was the first and the only symptom for years. The simultaneous presence of marginal erythema (45% of cases), subcutaneous edema (30%), and pharyngo-laryngeal edema (10%) facilitated the diagnosis of an abdominal attack due to C1-INH-HAE. Abdominal attacks manifested with recurrent acute abdominal symptoms lasting 2 to 5 days. The disease course was characterized by the phase of progressive prodromal symptoms followed by peak symptoms and spontaneous symptom resolution. Abdominal imaging often revealed abundant ascites and limited bowel edema. In 60 cases (22%), the diagnostic difficulties resulted in exploratory laparotomy, which was inconclusive in 48 patients (80%). The attacks usually subsided within 2 hours from the administration of recommended drugs (plasma-derived C1-INH , recombinant C1-INH or icatibant). We conclude that recurrent abdominal attacks lasting a few days and resolving spontaneously were common symptoms of C1-INH-HAE. Abdominal imaging revealed transitional fluid or bowel edema. The effectiveness of recommended drugs as plasma-derived C1-INH, recombinant C1-INH or icatibant confirmed the diagnosis.

Key words: *hereditary angioedema, C1-inhibitor, bradykinin, abdominal attacks, abdominal imaging, computed tomography, subcutaneous edema, pelvic ultrasound*

INTRODUCTION

Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is a rare inherited autosomal dominant disease caused by C1-inhibitor deficiency due to a heterogeneous mutation of the *C1-INH* gene (*Serping1*) (1-6). The mutation results in a significant reduction in the activity of C1-INH, the main inhibitor of the kinin system. Alterations in the kinin system facilitate the release of bradykinin (BK), which is the major mediator of angioedema in C1-INH-HAE, leading to numerous disturbances in the homeostasis of the body (7-14).

C1-INH-HAE occurs in two phenotypic variants: type I and type II HAE. Type I HAE is characterized by a significant reduction in C1-INH functional activity and concentration (>50% of lower limit). It is diagnosed in over 80% of cases. In type II HAE, C1-INH activity is significantly reduced but its serum concentration remains normal or elevated. It is found in approximately 20% of patients (1-3, 5).

Angioedema in patients with C1-INH-HAE has characteristic clinical features. The attacks are recurrent, appear with different frequency and may occur in multiple locations, last from 2 to 5 days, and affect the subcutaneous tissue (usually the hands, feet, and face) or submucosal tissue (most commonly the gastrointestinal tract, and less often the airways which may be life-threatening). Angioedema typically occurs over a limited area. It progresses slowly (usually over a few hours), reaches the maximum intensity usually on the second day, and then resolves spontaneously within next 2 to 3 days. The symptoms are not accompanied by itching or hives and are resistant to antihistamine and corticosteroid treatment (1-3).

Submucosal edema in patients with C1-INH-HAE often constitutes a diagnostic and therapeutic challenge. The

symptoms can be life threatening in the case of respiratory tract involvement (*e.g.*, laryngeal edema) and in the case of gastrointestinal swelling. They constitute always a diagnostic problem mimicking acute abdomen, often leading to misdiagnosis, unnecessary surgery, various complications such as intestinal obstruction and hypovolemic shock due to excessive fluid loss from the peritoneal cavity (15-17).

Abdominal attacks in patients with C1-INH-HAE are common, the awareness of these symptoms is insufficient among general practitioners, surgeons, and emergency department doctors who deal with undiagnosed HAE patients reporting an edema attack (18-20).

Bradykinin-mediated submucosal swelling in the gastrointestinal tract is a segmental edema caused by the activation of bradykinin B_2 and B_1 receptors in the capillary endothelium following capillary dilatation, increased permeability, and contractile effect on smooth vascular muscles. In the case of HAE abdominal attacks, a spasmodic or contractile effect of bradykinin on the intestinal smooth muscles can be seen, causing colic pain and an increase of intestinal peristalsis in the swollen area (11, 21-23).

Research performed in recent years proved that not only BK and kinin generation process, but also products of BK degradation (11, 21) are important for understanding pathophysiology of the diseases in which BK is involved (22, 24). These processes remain in relation with many other systems activation, such as the complement system, contact, coagulation, fibrinolysis and renin-angiotensin-aldosterone system (RAAS).

The aim of the study was to investigate the difficulties in recognition of abdominal attacks in patients with diagnosed C1-INH-HAE. The diagnostic value of medical history, the course of the attack, abdominal imaging, as well as the efficacy of recommended therapies were analyzed.

MATERIAL AND METHODS

The study group included 274 patients with types I and II C1-INH-HAE and abdominal attacks. Participants were selected out of the 322 symptomatic patients treated at a HAE center in the University Hospital in Cracow (Cracow, Poland). The diagnosis of C1-INH-HAE was established based on medical history, physical examination during angioedema attacks, and laboratory testing. Laboratory diagnosis of C1-HAE type 1 was established on the basis of a decrease in the serum C1INH concentration and plasma functional activity of C1INH (<50% of the normal value), and C1-INH HAE type 2 based on low C1 INH functional activity (<50% of the normal value) with normal or elevated C1 INH levels (6).

C1-INH functional activity was determined using the Berichrom C1-inhibitor assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Serum C1-INH levels were measured by nephelometry (Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Descriptive statistics for the examinated group were expressed as mean with range or standard deviation.

In patients included into the study a retrospective analysis of the history, the symptoms, patients diary, course of moderate and severe abdominal attacks (15) from onset to resolving of symptoms, analysis of trigger factors and prodromal symptoms, complications as well as the results of abdominal and pelvic imaging done during abdominal attack, the results of exploratory laparotomy performed in some of patients and the efficacy of treatment was taken into account.

The evaluation of the abdominal attacks of the patients based on medical history, medical records/documentations in the course of emergency care during abdominal attacks, with an assessment of treatment efficacy, on analysis of patients diary completed in measure interview needs as well as on the evaluation of abdominal imaging during abdominal attack.

Imaging examinations of the abdominal cavity and small pelvis (ultrasound examination and CT scan) performed in the studied patients with C1-Inh HAE during acute abdominal attacks often in a serious condition, were subjected to retrospective analysis in order to extend the diagnosis in doubtful cases.

The most often performed was ultrasound examination as the most available and regardless of the patient's condition study, the most accessible and fastest, which can be performed at the bedside and does not show any harm to the patient and can be performed repeatedly allowing to monitor the patient's condition. and the effectiveness of treatment.

A CT scan was performed in some case of clinical doubts as to the causes of clinical symptoms in patients in order to exclude

Table 1. Clinical characteristics of patients with abdominal attacks in the course of hereditary angioedema due to C1 inhibitor deficiency (n=274).

Parameter		**Value**
Sex, n	Male	84
	Female	190
Age, years, mean (range)		36 (4-70)
HAE, n (%)	Type I	247 (90)
	Type II	27 (10)
Positive family history, n (%)		218 (80)
Site of the first HAE attack, %	Abdomen	49
	Subcutaneous edema	41
	Oropharyngeal edema	10
Abdominal or pelvic ultrasound/CT during abdominal attack, n (%)		56 (20)
Exploratory laparotomy during HAE attack, (%)		58 (21)
Serum C1-INH levels[a], mg/dl, mean (SD)	Type I HAE	0.06 (0.025)
	Type II HAE	0.04 (0.224)
C1-INH functional activity[b], %, in type I and II HAE		17.6 (14.53)

C1-INH, C1 inhibitor; HAE, hereditary angioedema; [a]reference range: 0.2–0.39 mg/dl; [b]reference range: 70–130%.

various other reasons, including surgical ones of the acute abdomen. This examination exposes the patient to radiation and cannot be performed to monitor the patient's condition, but only to diagnose the causes of the symptoms. A CT scan may be performed at the HED if the patient's condition is clinically stable and depending on the HED's ability to perform such an examination.

RESULTS

Of the 322 patients with C1-INH-HAE treated and lasting under constant medical care in our center, the recurrent abdominal attacks occurred in 274 (85%). The group included 190 women and 84 men (mean age, 36 years (range, 4–70 years)). There were 41 children or adolescents aged 4 to 18

Table 2. Clinical characteristics of patients depending on the time at onset of abdominal attacks in the course of hereditary angioedema due to C1 inhibitor deficiency.

Abdominal attacks	**No. of patients** (%)	**Sex** n	**Age at HAE onset,** mean (SD)	**Age, range,** (years)	**Type I HAE, n** (%)	**Positive family history, n** (%)
At onset of HAE	133 (49)	Female, 88 Male, 45	10.9 (6.8)	4–70	128 (96)	109 (82)
After 3–30 years of HAE onset	141 (51)	Female, 94 Male, 47	14.5 (10)	12–36	129 (91)	109 (77)

C1-INH, C1 inhibitor; HAE, hereditary angioedema.

Table 3. Results of explorative laparotomy depending on the presence of abdominal attacks and other symptoms.

Patients	**No. of patients**	**Patients undergoing laparotomy,** n (%)	**Laparotomy findings**
Patients with C1-INH-HAE and abdominal attacks	274	60 (21)	Appendicitis (n=9) Intussusception (n=3) Perforation (n=1) Inconclusive findings (n=47; 78%)
Patients with C1-INH-HAE without abdominal attacks	48	5 (10)	Appendicitis (n=5; 10%)
Asymptomatic patients with C1-INH deficiency	19	1 (5)	Appendicitis (n=1; 5%)

Abbreviations: see *Table 1*.

Table 4. The course of abdominal attacks in patients with hereditary angioedema due to C1 inhibitor deficiency.

Phase of abdominal attack*	**Time**
1. Prodromal symptoms	
Erythema marginatum in 45% cases. Other types of subcutaneous edema in 30% of cases. Other symptoms include fatigue, sleepiness, aggressiveness, irritability, tingling, numbness, myalgia.	from few hours to 24 hours before an attack
2. Initial progressive phase	
Recurrent moderate to severe colic pain (100% of cases), strong flatulence (100%), vomiting (65%), and diarrhea (38%). In 30% of cases the abdominal symptoms were accompanied by external edema. Abdominal imaging may reveal the increasing volume of ascites or limited bowel edema that resolve spontaneously after a few hours.	up to 12 hours
3. Peak symptoms	12–24 hours
4. Gradual spontaneous resolution of symptoms	over 48–96 hours
*Relief of symptoms in each phase can be achieved with plasma-derived C1-inhibitor concentrate or icatibant (inhibitor of bradykinin B_2 receptor).	

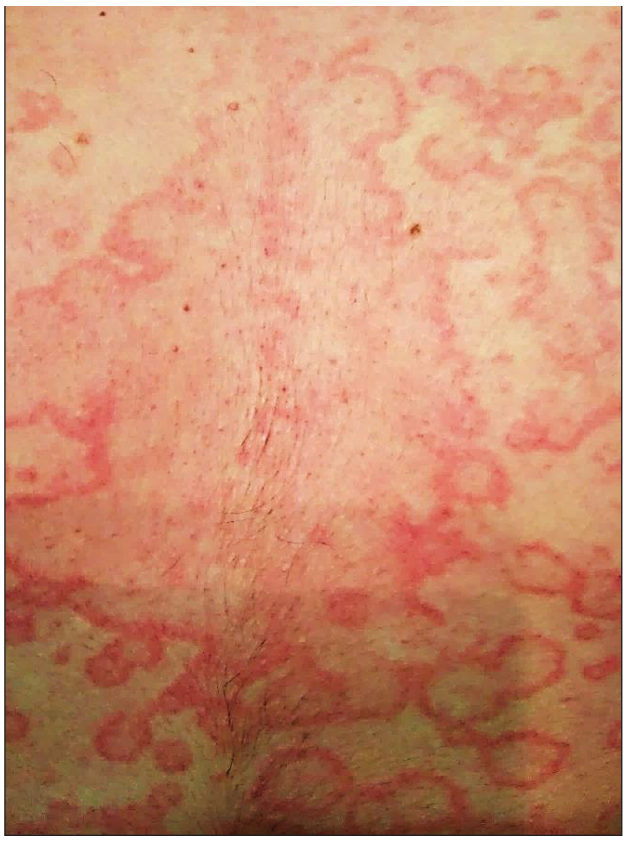

Fig. 1. A photograph of erythema marginatum in patient with HAE during the angioedema attack (erythematous, polycyclic, serpentine skin lesions).

years. The time period from the first angioedema attack to the diagnosis of HAE ranged from 2 to 62 years, mean - 9 years. 80% of patients had a positive family history of HAE. Abdominal attacks as the first HAE symptom were reported in 49% of cases. The clinical characteristics of the study group are presented in *Table 1*.

The clinical analysis allowed us to divide patients with abdominal attacks in the course of C1-INH-HAE into 2 groups. The first group included 133 patients in whom an abdominal attack was the first symptom of the disease (and remained the only symptom for many years in 3 cases). The second group included 141 patients in whom abdominal attacks occurred 3 to 30 years after angioedema attacks at other sites. The type of HAE, sex, and positive family history were not associated with the incidence of abdominal attacks in patients with C1-INH-HAE. Patients with an abdominal attack at the onset of HAE were younger than the remaining patients (*Table 2*, group A) suggesting that an abdominal attack can be the first symptom of the disease in younger children.

The observation period prior to diagnosis was based on anamnesis and medical records. While the period after HAE diagnosis was based on the patient's diary, emergency medical records, and his own medical records (check-ups and attack tests) taking into account the frequency and severity of the seizure a scale of 1–3 (15) as well as a result of the effectiveness of the recommended treatment. The self-observation period of patients after diagnosis ranged from 2 to over 30 years.

In all patients, abdominal attacks were accompanied by recurrent acute colic at different sites and pain of moderate to severe intensity. Severe flatulence was present in 75% of patients; vomiting or nausea, in 72%; and diarrhea, in 45%. Patients with severe attacks often reported strong weakness and reduced blood pressure.

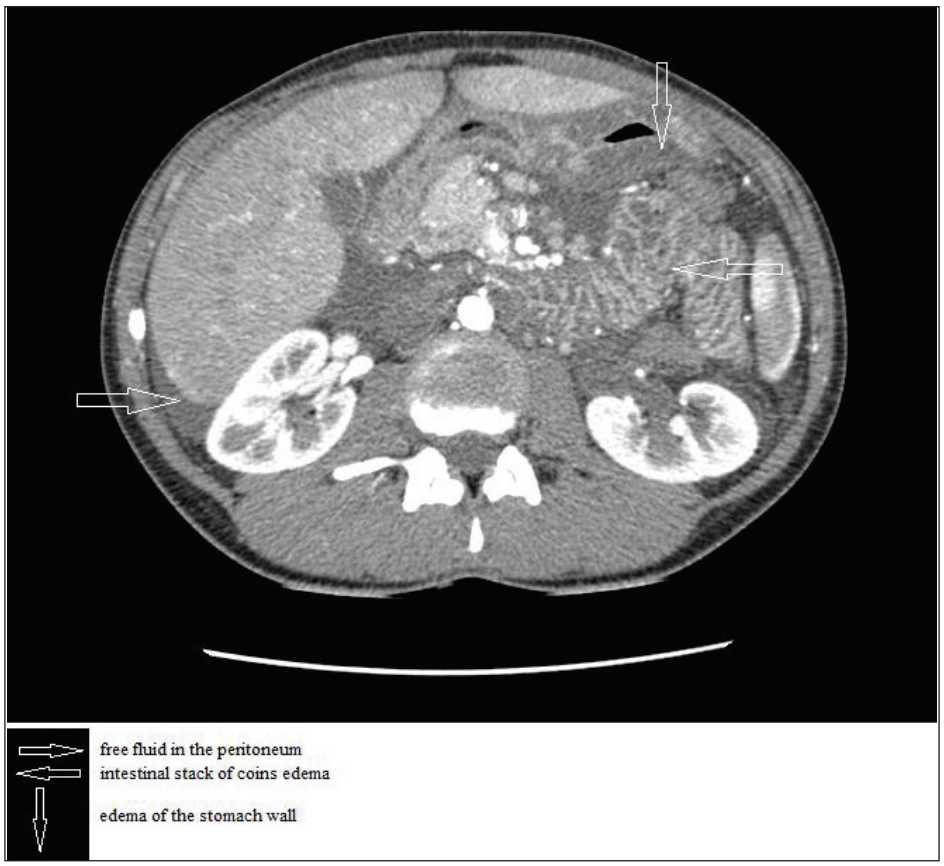

Fig. 2. An abdominal computed tomography scan showing intestinal swelling and free peritoneal fluid in a patient with angioedema.

In some patients, the prodromal symptoms of varying severity sometimes appeared a few dozen hours before the attack. Erythema marginatum developed in 45% of cases, while 35% of patients reported fatigue, somnolence, irritation, aggressiveness, numbness, tingling, and muscle pain as symptoms that preceded the onset of edema.

In some cases, a medical interview revealed some triggering factors. In 40% of patients, abdominal attacks were induced by trauma, stress, infection, poor nutritional habits (heavy meal or starvation), and significant physical effort. Some patients indicated that the attacks were provoked by certain food products such as milk, eggs, fish, legumes, or spices, but food challenge tests did not confirm any food allergy. The elimination of the suspect food usually reduced the frequency of abdominal attacks in these cases, suggesting food intolerance.

In 8 cases in whom the presence of inflammatory foci in the gastrointestinal tract has been confirmed (*Helicobacter pylori* in 4 cases, parasitic infection in 2 cases: Ascaris/Toxocara and dysbiosis, in 2 cases) elimination of them caused a significant reduction in attack severity from severe to moderate (from 3 to 1–2 in scale 1–3) and reduction of attack frequency (from 2–3/month to 1 for 1–2 month observed in 1 to 6 months after the treatment of the inflammatory focus.

An exploratory laparotomy in an abdominal attack was performed in 60 patients enrolled in the study due to poor efficacy for up to 2 hours of the drug recommended in an abdominal attack in patient with C1-INH-HAE (pd C1INH, recombinant C1INH or icatibant) and the resulting necessity to exclude another cause of the attack.

The analysis of the laparotomy results allowed in 15 cases (25%) to establish the cause of the abdominal attack (*Table 3*) and confirm the need for laparotomy due to appendicitis in 9 cases, occlusion in 4 cases and perforation in 2 cases.

In 47 cases (78%), the findings were inconclusive except for 18 patients in whom excessive free peritoneal fluid was revealed and evacuated during the procedure.

The results of explorative laparotomy in patients with C1-INH-HAE and abdominal attacks were compared with those in patients with C1-INH-HAE without abdominal attacks and with those in asymptomatic patients with C1-INH deficiency. The comparison is presented in *Table 3*. The cause of laparotomy in all patients without abdominal attacks and in asymptomatic patients was acute appendicitis.

Abdominal and pelvic ultrasound or computed tomography (CT) during an abdominal attack were performed in 56 of the 274 cases (20%). The imaging studies revealed a large amount of free abdominal fluid and limited bowel swelling in 60% of patients (*Fig. 2* and *Fig. 3*). In each case, imaging findings were usually present only in the first hours of progressive severe abdominal symptoms up to 12 hours and disappeared with the spontaneous resolution of symptoms on day 2 or within 1 to 2 hours after treatment with plasma-derived C1-INH infusion or icatibant.

Based on our results, we identified the characteristic features of abdominal attacks in patients with C1-INH-HAE (*Table 4*), which may facilitate the diagnosis of an abdominal attack. We described the 4 characteristic phases of an abdominal attack due to C1-INH-HAE. First, there is the phase of prodromal

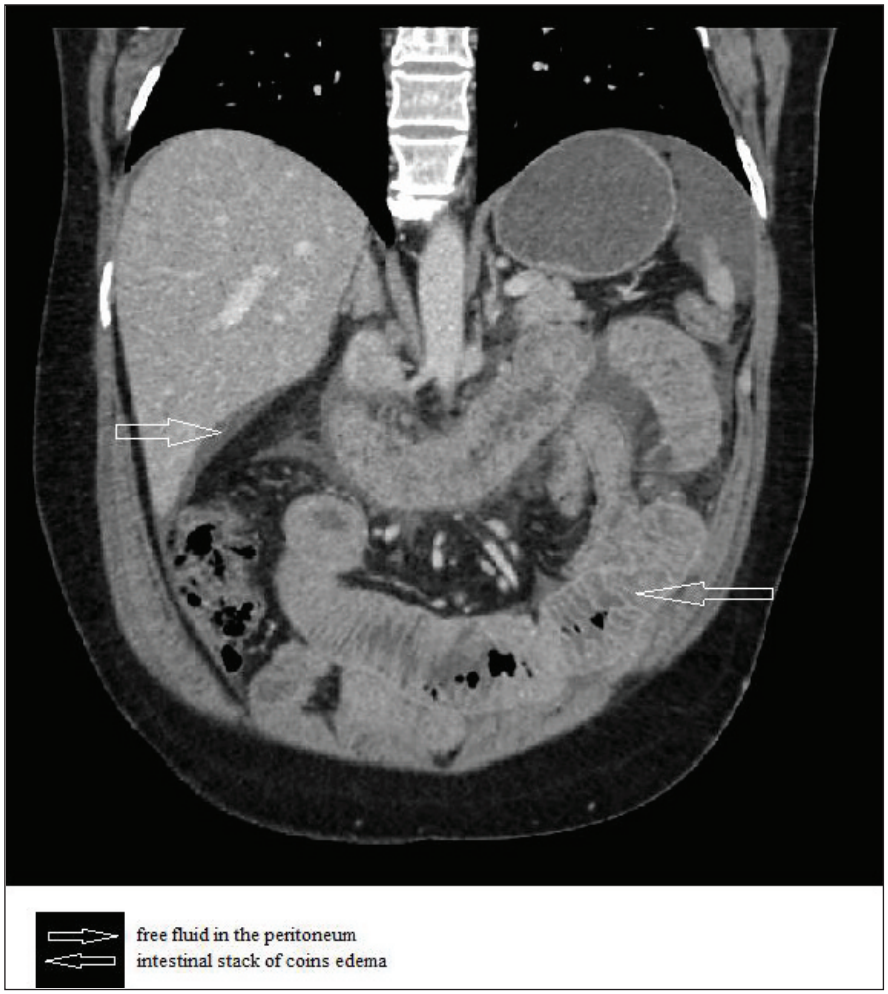

Fig. 3. A pelvic computed tomography scan showing intestinal swelling in a patient with angioedema.

symptoms, most typically erythema marginatum (*Fig. 1*). This is followed by the initial progressive phase lasting up to 12 hours, with recurrent colic or crampy pain of increasing severity and usually strong flatulence. In cases of abdominal attacks with very severe pain and distension (especially associated with excessive peritoneal fluid), severe weakness and lower blood pressure were observed. In 30% of patients, the simultaneous presence of abdominal symptoms and subcutaneous swelling was reported.

These additional symptoms together with erythema marginatum and a positive family history may be helpful in recognizing abdominal attacks due to HAE. The phase of peak symptoms lasts from 12 to 24 hours and is followed by gradual resolution of symptoms over 2 to 3 days.

The effectiveness of the recommended drugs, such as plasma-derived C1-INH and icatibant, confirmed the abdominal HAE attack in all participants. The symptoms usually subsided within 1 to 2 hours and resolved completely within 1 to 2 days. The 4 phases are summarized in *Table 4*.

DISCUSSION

We reported the results from a long-term follow-up of a large population of patients with C1-INH-HAE. Our findings confirm the frequent occurrence of abdominal attacks (85%) in these patients and indicate that abdominal attacks are a common, typical symptom of this disease (1, 6, 18-20).

The frequency of abdominal symptoms is close to that reported for subcutaneous angioedema (86.7%), which is considered the classic symptom of C1-INH-HAE. Our results are also consistent with the recent reports of numerous other authors (15-20, 25, 26). Like subcutaneous angioedema, abdominal attacks constitute a significant problem in patients with C1-INH-HAE because they are highly prevalent and reduce the patients' quality of life. However, the burden of abdominal attacks seems to be even higher because each attack is diagnostically challenging and may be life threatening. Moreover, emergency department doctors or surgeons often have insufficient expertise to diagnose the edema of the internal organs in the course of HAE (15-19, 27-30).

The diagnosis of acute abdominal symptoms in patients with C1-INH-HAE is particularly challenging if abdominal attacks are the first, and sometimes the only, symptom of the disease (as observed in 49% of patients in our study). In such cases, the diagnosis may be delayed for many years. Extensive experience in managing patients with C1-INH-HAE is required to avoid misdiagnosis that could lead to unnecessary surgical procedures and complications, such as gastrointestinal obstruction or perforation, or hypovolemic shock due to the rapid movement of fluid from the vascular placenta to the tissue or abdominal cavity during the angioedema attack (15, 16, 18, 19, 29, 31-34).

Our findings suggest that abdominal attacks are more common in younger children with C1-INH-HAE however they are often misdiagnosed. Moreover, they may cause diagnostic difficulties in patients with acute abdominal symptoms and result in long delays in the diagnosis of the underlying disease for many years (2).

According to several studies investigating bradykinin-mediated angioedema in patients with C1-INH-HAE, the deficiency or dysfunction of C1-INH, the main systemic inhibitor of the kinin system, leads to an uncontrolled increase of bradykinin levels. Moreover, based on available research, an abdominal attack is caused by a local bradykinin-mediated submucosal swelling of the intestines and is a local symptom of a systemic activation process (6, 35, 36). Finally, BK binds its B_2 receptors to predisposed endothelial cells, thus causing their activation and activation of bradykinin B_1 receptors, initiating the slow development of limited angioedema.

Of note, in the case of an abdominal attack in the course of HAE, the stimulation of bradykinin receptors leads not only to an increase of capillary permeability but also to an increase in intestinal smooth muscle contractility and peristalsis, thus inducing severe abdominal pain (11, 21, 29-32, 35-37).

Symptoms of acute abdomen pain requires exclusion of other not only most common reasons. Also rarely occurring situations, like for example the altered dopamine signaling in the course of chronic epigastric pain syndrome (CEPS) (38), or the side effects of biopolymers used in the treatment of organ prolapse, deposited in pelvic or abdominal cavity (39).

Our current study as well as reports of other authors indicate that the diagnosis of an abdominal attack in patients with HAE can be greatly facilitated if the clinician has the appropriate knowledge of the characteristic clinical features. These are assessed on the basis of medical history, the presence of prodromal symptoms (especially erythema marginatum), the presence of simultaneous external edema, and the characteristic course and duration of symptoms (2, 3, 6, 16-18, 20, 30). Abdominal imaging is a particularly useful tool to diagnose abdominal attacks in patients with HAE. This refers especially to the easily accessible and noninvasive abdominal and pelvic ultrasound examination in urgent cases. In contrast, CT is often difficult to perform in urgent cases, although it offers greater precision than ultrasound. (2, 18, 20, 25, 30, 32, 40-46).

Ultrasound examination allows clinicians to monitor the course of the abdominal attack and the efficacy of treatment. Abdominal ultrasound should be the first-choice diagnostic test in patients with C1-INH-HAE and abdominal attacks. It allows an identification of typical dynamic changes in the abdomen, such as the presence of free fluid, changes in fluid volume, and edema of the intestines or another internal organ (2, 17, 37, 46). However, our study showed that imaging tests were performed only in 20% of patients, which confirms that they are still rarely used for the diagnosis of abdominal attacks in the HAE population.

In doubtful cases, an inconclusive abdominal ultrasound or the lack of improvement despite treatment should prompt the use of a more precise contrast-enhanced abdominal and pelvic CT. Computed tomography should be reserved for cases of abdominal attacks that are particularly challenging in diagnostic terms. This is important considering the high prevalence of abdominal attacks in patients with HAE, which may occur even several times a month. Advanced imaging may help identify another cause of abdominal swelling and related symptoms, thus facilitating timely diagnosis and treatment (42-45).

A referral of patients with C1-INH-HAE for exploratory laparotomy during an abdominal attack is always difficult and should consider the results of abdominal imaging studies. The problem of unnecessary exploratory laparotomies performed during abdominal attacks in patients with HAE was described previously (18, 20, 25, 46). Our study confirmed that exploratory laparotomies are performed too often in C1-INH-HAE patients with abdominal attacks - they were justified only in a minority of cases with appendicitis, intussuspection or perforation of the intestine. Moreover, redundant laparotomies were shown to be much more common in C1-INH-HAE patients with abdominal attacks than in those with HAE without abdominal attacks or in asymptomatic patients with C1-INH deficiency.

An abdominal attack in patients with C1-INH-HAE mimics an acute abdomen and each time requires the exclusion of the various others possible causes provoking acute abdominal symptoms, such as appendicitis, gall bladder inflammation or gallstones, gastric ulcer, ileitis, acute ovarian cyst, renal calculi, mesentery inflammation, portal vein thrombosis, ectopic pregnancy, or porphyria. In these cases, abdominal CT may be particularly helpful, although it may be difficult to perform during an acute attack (2, 18, 19, 42, 45).

In difficult cases, the administration of plasma-derived C1-INH or bradykinin B_2 receptor inhibitor icatibant, in patients with confirmed or suspected diagnosis of C1-INH deficiency could spare a patient laparotomy (6, 27, 47-50). The drugs are usually effective within 1 hour of administration. They should stop the progression of symptoms and lead to their gradual resolution. The poor efficacy of these drugs or recurrence of abdominal symptoms after a few hours (possibly due to complications) requires hospitalization until complete and permanent resolution of abdominal symptoms is achieved. A surgical consultation and imaging follow-up is also needed to avoid complications.

In conclusions we have confirmed that recurrent, self-remitting abdominal attacks lasting 2 to 5 days are common in patients with C1-INH-HAE. They may occur as the first and the only symptom of the disease in some subjects. Marginal erythema, subcutaneous edema, positive family history, and laboratory-confirmed C1-INH deficiency facilitates the diagnosing of an abdominal attack in the course of HAE. Abdominal imaging with easily accessible ultrasound or more precise CT that reveals transitional fluid or bowel edema should be the diagnostic tests of choice in patients with a suspicion of an abdominal attack in the course of HAE.

The diagnosis of HAE abdominal attack is confirmed if the recommended treatment with plasma-derived C1-INH, recombinant C1-INH, icatibant, or the recently introduced - ecallantide-kallikrein inhibitor is effective. If the treatment is ineffective or symptoms recur after a temporary relief, the patient should be hospitalized and receive treatment under imaging monitoring until the attack has completely subsided.

Abbreviations: C1-INH, C1 inhibitor; C1-INH-HAE, hereditary angioedema due to C1-inhibitor deficiency; CT, computed tomography; HAE, hereditary angioedema.

Conflict of interest: None declared.

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Abdominal and pelvic imaging in the diagnosis of acute abdominal attacks in patients with hereditary angioedema due to C1-inhibitor deficiency

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Abstract

Introduction: Hereditary angioedema (HAE) is a rare inherited autosomal dominant disease caused by deficiency or dysfunction of C1 inhibitor (C1INH). Clinical symptoms include recurrent subcutaneous and submucosal angioedema of the internal organs. Abdominal attacks affect more than 90% of patients, are often misdiagnosed and result in unnecessary surgical procedures.

Aim: To analyse the utility of imaging studies (USG, CT) in patients with C1INH-HAE during an abdominal attack and remission.

Material and methods: We enrolled 40 patients with type I and II HAE (30 women, 10 men; mean age 39 years). The diagnosis of C1INH-HAE was based on patient and family history, significantly reduced values of C1INH serum level and activity. Abdominal and pelvic ultrasound were performed in patients within the first 6 h of the abdominal attack and repeated during remission. Moreover, 23 cases underwent abdominal or pelvic computed tomography during acute abdominal symptoms. The most common ultrasound and CT findings showed the transient presence of a significant amount of fluid in the free abdominal cavity and intestinal oedema during the symptom progression and spontaneously disappearing during the seizure in 90% and 50% of patients, respectively. CT revealed also an enlargement of the mesenteric lymph nodes as well as a fat stranding along the bowel wall thickening.

Conclusions: Ultrasound or CT imaging facilitates the diagnosis of the patient suspected of having an abdominal attack due to C1INH-HAE. They allow to identify transitional presence of an abundant fluid in the free abdominal cavity and intestinal swelling which spontaneously disappear with a symptoms attack.

Key words: abdominal imaging, bradykinin, C1 inhibitor, hereditary angioedema.

Introduction

Hereditary angioedema (HAE) is a rare inherited autosomal dominant disease caused by deficiency or dysfunction of C1 inhibitor (C1INH) [1–6]. There are two phenotypes of the disease. Type I affects about 85% of cases and is characterized by significantly reduced levels and functional activity of C1INH (by more than 50% compared with normal values). On the other hand, in type II, serum C1INH levels are normal or slightly elevated, and only the activity is largely reduced. The clinical course and symptoms of the disease are similar in both types. Symptoms include recurrent self-limited subcutaneous oedema (typically of the hands, feet, face, and genitals); submucosal oedema affecting the internal organs such as the upper respiratory tract (throat, larynx), which may be life-threatening; or gastrointestinal oedema manifesting as recurrent abdominal pain, often mimicking acute abdomen. Oedema is caused by hereditary C1INH deficiency due to Serping1 gene mutation, which predisposes these patients to bradykinin overproduction, which

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induces swelling reactions due to various stimuli [7–9]. Abdominal symptoms constitute a significant diagnostic challenge, with the necessity to exclude numerous other causes of acute abdominal pain. Angioedema attacks at other sites are rare and may affect the urinary tract (bladder, urethra, kidneys), musculoskeletal system as well as pericardial or pleural cavity. Attacks may also present with neurological manifestations such as headaches, transient vision loss, and migraine-like symptoms [5, 6].

Abdominal attacks constitute an important problem in HAE because they affect more than 90% of patients and occur even up to 2 to 3 times a month. They may be the first manifestation of angioedema in patients with C1INH-HAE and may remain the only symptom of the disease for many years [5, 10–13]. They often lead to significant delays in accurate diagnosis.

Acute abdominal attacks are common in the general adult population as well as in paediatric patients [5, 14]. Each time, it is necessary to exclude other possible causes, such as appendicitis, diverticulitis, sigmoiditis, mesenteric lymphadenitis, intussusception, bowel obstruction, polycystic ovary syndrome, ovarian or testicular torsion, and intestinal bleeding or ischemia [3, 5, 10]. The diagnosis of an abdominal attack in HAE is based on medical history, including C1INH deficiency confirmed by a laboratory test (significant reduction in C1INH serum level and C1INH activity in plasma compared with normal) [4, 15]. The deficiency may be accompanied by reduced C4 level, especially during the attack. Patients may report abdominal attacks lasting several days and resolving spontaneously after 3 to 5 days or after C1INH administration. A positive family history is also commonly reported [3, 5, 6].

The diagnosis of patients with C1INH-HAE and an abdominal attack is a considerable challenge at emergency, surgical, and gastroenterological units, which often results in unnecessary surgical procedures such as exploratory laparotomy [3, 5, 10, 12, 16–20]. Acute abdominal attacks in the course of HAE often manifest with acute abdominal pain with cramps, progressing over time and reaching the highest severity after several hours from onset without concomitant peritoneal symptoms. Pain is often accompanied by nausea, vomiting, severe flatulence, or less frequently, diarrhoea. Patients may also present with significant weakness, most often caused by the presence of excess peritoneal fluid due to hypovolemic shock [5, 21].

In patients with confirmed C1INH deficiency, the diagnosis of an abdominal attack may be aided by the administration ex juvantibus of plasma-derived C1INH, recombinant human C1INH, bradykinin B2 receptor antagonist – icatibant, or plasma kallikrein inhibitor ecallantide or also fresh frozen plasma. The effectiveness of these drugs within 1 h from administration confirms an abdominal attack in C1INH-HAE [3, 5, 22].

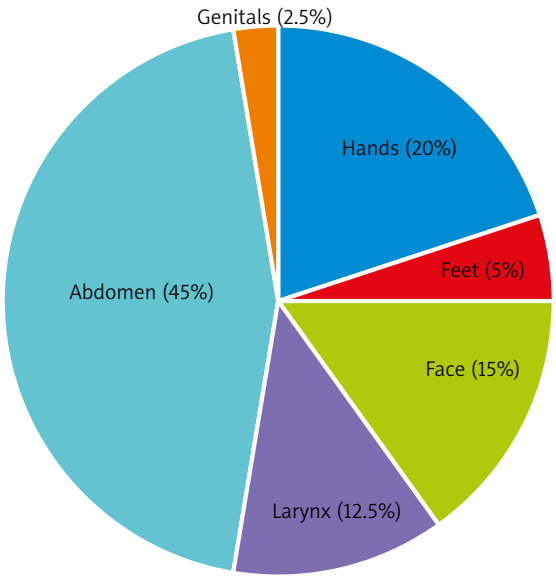


Figure 1. Parts of the body affected by edema during the first hereditary angioedema attack. Data presented as percentage of cases (n = 40)

Aim

The aim of this retrospective study was to assess the diagnostic utility of abdominal and pelvic imaging (ultrasound, computed tomography (CT)) in patients with C1INH-HAE during an abdominal attack and remission. We also aimed to assess data from medical history and physical examination performed during an attack to identify any potential criteria that could aid the diagnosis of HAE attack, facilitate the interpretation of imaging studies, and help assess patient eligibility for ultrasound or CT imaging during an attack.

Material and methods

The study included 40 patients with C1INH-HAE and abdominal attacks (30 women and 10 men; mean age: 39 years; range: 19–70 years). The diagnosis of C1INH-HAE was based on the presence of previous subcutaneous or submucosal angioedema attacks, a positive family history, and the measurement of plasma C1INH activity, serum C1INH and C4 concentration.

Type 1 C1INH-HAE was diagnosed in 34 patients on the basis of a reduction of serum C1INH concentration and plasma C1INH activity below 50% as compared to normal values. Type II C1INH HAE was diagnosed in 6 patients with normal value of serum C1 INH concentration and plasma C1INH activity below 50% as compared to the normal limit – according to standard criteria [2, 5, 15]. Diagnostic laboratory studies were performed during remission using the nephelometric method with a BN100 Nephelometer (Dade Behring). Functional C1INH activity was measured in plasma with the colorimetric kinetic method, using a chromogenic assay (Berichrom C1-Inhibitor and Complement Reagents) and Behring Coagulation Timer analyzer (both Dade Behring).

Of the study group, 30 (75%) patients had a positive family history. The first angioedema attack occurred be-

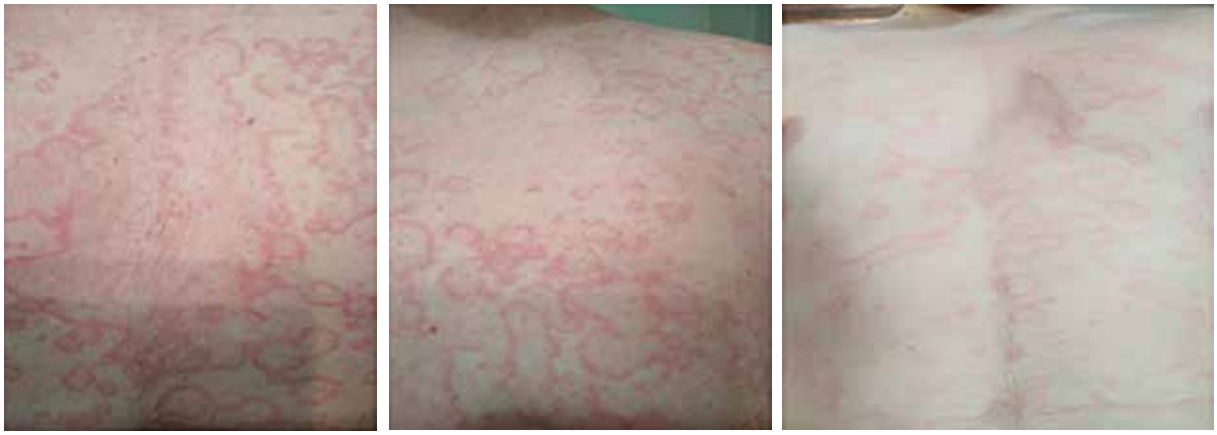


Figure 2. Erythema marginatum

tween the age of 2 and 29 years. The diagnosis of HAE was established 1 to 41 years after the first attack. Organ involvement at the first episode (Figure 1) was as follows: abdomen in 18 (45%) patients, hands and feet in 10 (25%), face in 6 (15%), larynx in 5 (12.5%), and genitals in 1 (2.5%) patient. Moreover, 19 patients (47.5%) developed erythema marginatum (Figure 2) before the attack and independently of the site of skin involvement (most often on the chest). However, it resolved spontaneously during the attack.

We retrospectively assessed 84 ultrasounds of the abdominal and lower pelvic regions. Ultrasound examination was performed in patients during an abdominal attack and remission. In 10 patients, imaging studies were performed more than once (2–9 times) during different attacks. Moreover, we assessed abdominal and pelvic CT scans obtained simultaneously with ultrasound in 23 patients during acute abdominal attacks. This retrospective analysis covers imaging tests that were performed during approximately 15 years at different diagnostic imaging units by different clinicians.

Results

The results of this retrospective analysis of imaging tests performed during acute abdominal attacks are presented in Figures 3, 4 A, B, 5 A, B and 6.

Abdominal and pelvic ultrasound performed in the first hours of acute abdominal attacks (Figure 4 A) in 36 (90%) patients revealed free peritoneal fluid. In some patients, low fluid volume was present in single peritoneal pouches in the pelvis, while in others, diffuse fluid accumulation was observed in the peritoneal cavity and additionally in several pouches, most commonly the hepatorenal recess, subhepatic, and pelvic peritoneal space. Segmental bowel wall thickening was much less common (identified in about 30% of patients). In 2 cases, the only abnormality on ultrasound was mesenteric lymph nodes, although without enlargement. In all patients, an ultrasound performed at day 3 of symptom remission revealed resolution of all abnormalities observed during the attack. A comparison of ultrasounds obtained several times during different attacks showed differences in findings in terms of the site and extent of intestinal oedema or fluid volume. Medical history confirmed that the disease course and severity of symptoms also differed between these individual episodes.

Abdominal and pelvic CT performed during an attack (Figure 4 B) showed similar abnormalities to those revealed by ultrasound, but it enabled a more accurate assessment. As with ultrasound, the most common finding was free peritoneal fluid (80% of patients). However, the presence of intestinal oedema was more frequent and more easily identified by CT scans. It also outperformed

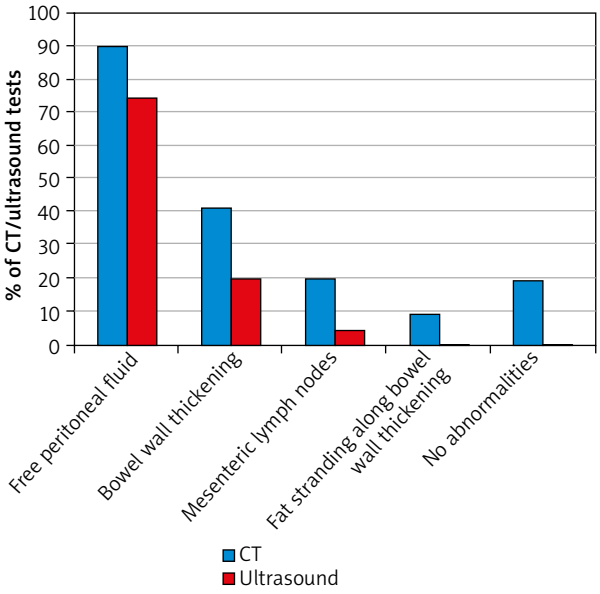


Figure 3. Abdominal and pelvic ultrasound and computed tomography finding during acute abdominal attack in the course of hereditary angioedema

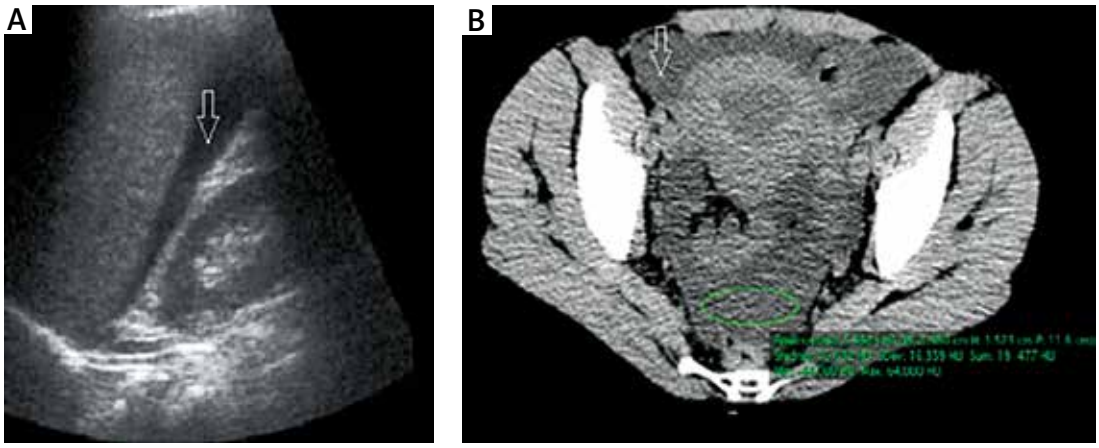


Figure 4. Free peritoneal fluid (arrow) on ultrasound (**A**) and computed tomography (**B**)

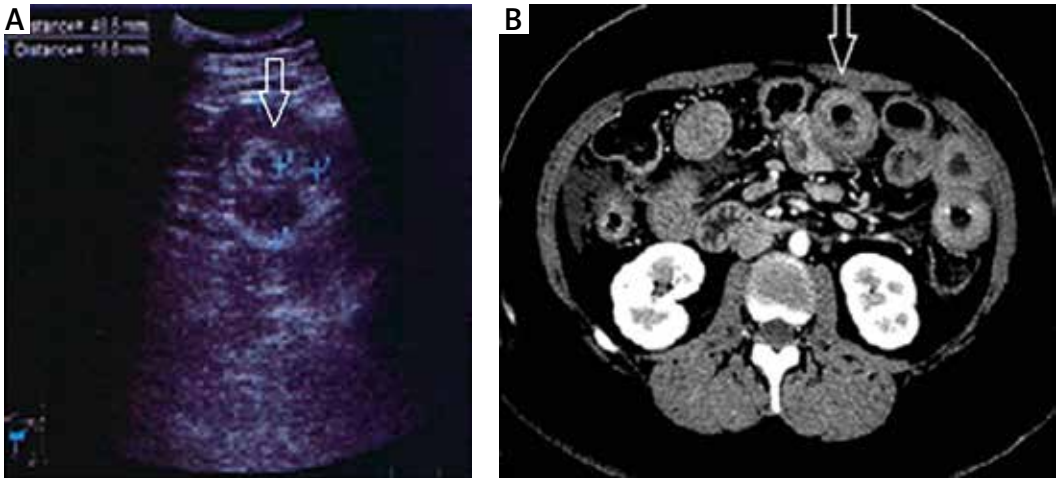


Figure 5. Bowel wall thickening (arrow) on ultrasound (**A**) and computed tomography (**B**)

ultrasound in terms of assessing the morphology of the intestinal wall and mucosal swelling (such as assessment of circular wall thickening, bowel wall stiffness, or multifocal oedema (e.g., affecting several bowel loops)). Finally, CT also enabled a more detailed evaluation of lymph nodes and fat stranding along bowel wall thickening (which is not visible on ultrasound).

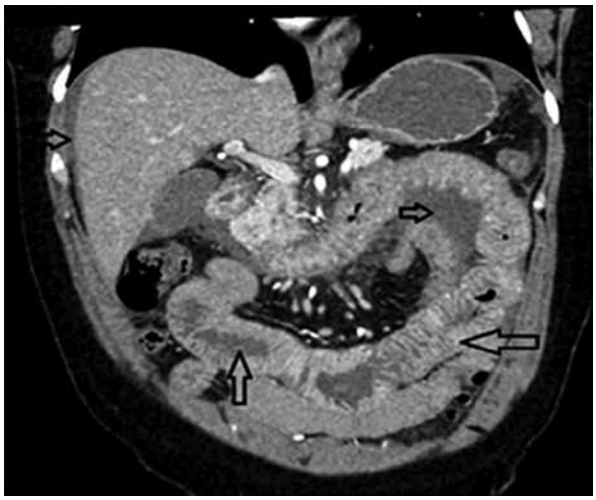
Peritoneal fluid on ultrasound is typically homogeneous and lacks echogenicity, while CT reveals low density (approximately 5–20 jH). A laboratory analysis of intraoperative fluid performed in 5 patients revealed the features of a transudate, water-like, and sterile fluid with low neutrophil and mononuclear counts.

Bowel wall thickening involved various segments, most commonly, the loops of the jejunum, followed by those of the ileum, duodenum, and colon. Both ultrasound and CT revealed 2 distinct types of swelling (Figures 5 A, B and 6):

1) symmetrical segmental thickening of all small bowel wall layers, with high attenuation of the inner and outer layers representing the mucosa and muscularis propria, respectively, corresponding to the so-called Target sign. This radiologic appearance of the bowel wall thickening should be differentiated from intestinal lymphoma and inflammatory bowel disease, among other conditions.

2) Segmental thickening of the small bowel mucosal folds due to submucosal oedema of the folds that run perpendicular to the long axis of the bowel (so-called stack of coins sign) and due to intramural blood accumulation secondary to submucosal haemorrhage and oedema (so-called thumbprint sign), or diffuse bowel wall thickening. The differential diagnosis should include intestinal ischemia, Henoch-Schönlein purpura, or intramural haemorrhage (due to trauma, haemophilia, or anticoagulant therapy).

Cases with notable bowel wall thickening on CT also showed concomitant fat stranding suggesting oedema and hyperaemia of the adjacent fat tissue and vessels. These oedematous changes are segmental (self-limited)



⇐ Bowel wall thickening
⇒ Peritoneal and interloop fluid accumulation
⇑ Intestinal fluid

Figure 6. Computed tomography scan in a patient with abdominal attacks with C1INH-HAE

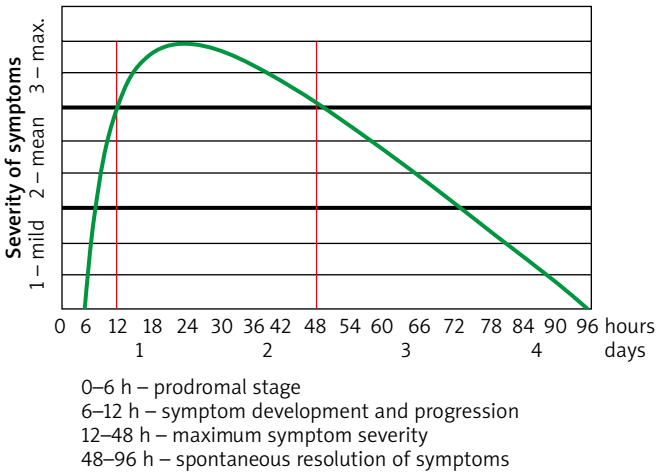


Figure 7. Stages and course of abdominal attacks in patients with hereditary due to C1 inhibitor deficiency

and can be observed only during acute symptoms as motility disorders without clinical features of bowel obstruction.

Another ultrasound and CT sign of an abdominal attack in our patients was nonspecific swelling of the mesenteric lymph nodes, although without enlargement, which resolved spontaneously after the attack. It was observed on ultrasound in 10% of patients, and on CT, in 30% (Figure 3).

A detailed medical history allowed us to establish several criteria suggesting an abdominal attack in a patient with HAE. In 12 (30%) patients, an abdominal attack was accompanied by external swelling. Some of the patients reported the attack to be induced by the following factors: an abundant meal, starvation, dietetic error, excessive physical exercise, and stress. In some patients, the attack was preceded by prodromal symptoms such as bad mood, sleepiness, and irritability. Moreover, 19 (47.5%) patients developed erythema marginatum several hours before the attack. It slowly progressed over time and resolved during the attack. Medical history revealed that in our patients the most acute abdominal attack usually manifested with recurrent acute pain, which worsened over time, reached maximum severity after several hours, and persisted for about 24 h, then spontaneously resolved gradually over 2 to 3 days or 1–2 h after treatment (Figure 7).

Recurrent pain was associated usually with nausea/vomiting in 34 (85%) patients, watery diarrhoea in 18 (45%) patients, and severe bloating in 30 (75%) patients. In addition, 6 (15%) patients reported considerable weakness with hypotension during acute attacks with vomiting, diarrhoea, and significant ascites. Symptoms persisted for 24 h. Finally, in some cases the administration ex juvantibus of plasma derived C1INH or fresh frozen plasma was reported to stop symptom progression within 1 h and to result in complete symptom resolution within a few hours in patients with C1INH-HAE.

The analysis of medical history, physical examination performed during progression of abdominal symptoms, as well as medical records revealed the following findings:

1) Several recurrent abdominal attacks in the past, often with recurrent ascites. They resolved spontaneously without treatment, usually gradually after 2 to 3 days from onset or gradually within several hours from C1INH or fresh plasma administration.

2) In 14 of the 40 (35%) patients, exploratory laparotomy was performed during the attack. In 8 cases, it revealed excess peritoneal fluid but did not identify the cause of the attack. In 5 cases, laparotomy revealed a concomitant cause of acute abdomen.

3) The analysis of additional laboratory tests performed in patients during an acute abdominal attack frequently revealed an increased white blood cell count and haematocrit, reduced activated partial thromboplastin time, and less frequently, highly elevated D-dimer levels (without radiologic signs of vascular coagulation). The least common finding was an increased C-reactive protein level.

As mentioned above, exploratory/diagnostic laparotomy was performed in 13 of the 40 patients (33%). In 8 cases, no surgical cause of acute abdominal pain was found. It only revealed the presence of free peritoneal fluid and, rarely, segmental bowel thickening. However, in 5 cases, concomitant causes of acute abdomen were found, including acute appendicitis in 3 patients, ruptured ovarian cyst in 1 patient, and duodenal ulcer perforation in 1 patient (perforation causing acute abdomen

occurred on the third day of recurrent abdominal attacks in the course of C1INH-HAE).

Discussion

Acute abdominal attacks and external swelling are the most common symptoms of C1INH-HAE.

According to the results of our research, attacks occur in more than 90% of patients with C1INH-HAE and constitute a considerable diagnostic challenge for emergency clinicians, surgeons, gastroenterologists, and gynaecologists, requiring a differential diagnosis with numerous other possible conditions presenting with acute abdomen [5, 10, 14, 17, 19, 20, 23–26].

Therefore, patients are commonly misdiagnosed and receive inappropriate treatment including unnecessary exploratory laparotomy [3, 5, 10, 12, 16–20, 23]. Finally, abdominal attacks cause long delays in diagnosis, even up to several years, especially when they are the only presenting symptom of HAE [11, 13, 19, 20, 27–31]. Therefore, numerous investigators have emphasized the clinical value of abdominal and pelvic imaging and the necessity to introduce these modalities into regular diagnostic workup of patients with abdominal attack in the course of C1INH-HAE [3, 5, 6, 23, 26, 32–34].

Our analysis of abdominal and pelvic imaging (ultrasound and CT) in patients with an abdominal attack in the course of C1INH-HAE revealed 2 characteristic findings, namely, the presence of free peritoneal fluid (in more than 90% of patients) and segmental bowel wall or mucosal thickening (in about 50% of patients). These observations are consistent with the results of other studies to date [5, 6, 10, 11, 17, 18, 27, 34–38].

In addition, evaluation of imaging findings as well as medical history data allowed us to identify several characteristic features of free peritoneal fluid. These included variable fluid volume over subsequent attacks, which correlated with pain symptoms, as well as its spontaneous resolution or resolution after ex juvantibus treatment [3, 5, 10, 22, 23]. According to Agostoni *et al.* [6] and the results of our findings, the appearance of fluid on ultrasound or CT imaging during an abdominal attack in patients with C1INH-HAE depends on its volume. Small fluid accumulation is often visible in the subhepatic/subsplenic region and always in the pouch of Douglas. On the other hand, larger fluid volume can be seen in the perisplenic region and between bowel loops (which are often oedematous and thickened). Freely floating loops suggest excessive fluid volume.

The presence of fluid during an abdominal attack in patients with HAE requires exclusion of other causes, such as dissemination of neoplastic disease, decompensated cirrhosis of the liver inflammatory diseases, nephrotic syndrome, protein-losing enteropathy, or mesenteric venous thrombosis. An important aspect to consider in the differential diagnosis is the rate of fluid accumulation and resolution. Significant ascites in a patient with an abdominal attack may be complicated by severe weakness. This results in hypovolemic shock if a large volume of fluid leaks into the intestines and peritoneal cavity, especially when accompanied by vomiting or diarrhoea (which can be easily established on the basis of medical history) [5, 10, 21, 22, 29, 34, 35, 37, 39]. In such cases, apart from excess free fluid in the abdomen or pelvis, imaging reveals also the leakage of watery fluid into the intestines, which results in watery diarrhoea seen in many patients during an attack.

As stated above, another characteristic radiologic finding in patients with C1INH HAE during an abdominal attack was segmental oedema of bowel wall or mucosal thickening, seen on ultrasound in 25% of patients and on CT in 50% of patients. It involved all layers of the bowel wall over a segment of more than 10 cm in length. Most often, it was localized in the small bowel, which is in line with the results of previous studies [5, 6, 33–35].

Exclusion of mesenteric venous thrombosis in patients with HAE and an abdominal attack is a common problem associated with the presence of elevated D-dimer levels, especially in attacks related to abnormalities of the kinin, coagulation and fibrinolysis systems in patients with bradykinin-mediated angioedema typical for patients with C1INH-HAE [10, 23, 40, 41].

About 20% of patients with acute abdominal attack did not present with typical findings on CT. This may be due to the fact that CT study was performed too early or too late, because the presence of fluid during an attack in patients with C1INH-HAE is transient and resolves spontaneously with other symptoms of the attack [5, 10]. In 8 cases, abdominal CT revealed single nonspecific and low amounts of fluid in the bowels. In 2 patients, the radiologic diagnosis of partial intestinal obstruction was not confirmed by subsequent surgical follow-up.

Follow-up ultrasound and CT performed during spontaneous remission or after treatment revealed complete resolution of abnormalities observed during an attack, which is in line with other studies [5, 6, 23, 33]. Therefore, recurrent fluid and its spontaneous resolution as well as segmental bowel thickening are considered to be the typical symptoms of an abdominal attack in patients with HAE. Medical history and records obtained from these patients often reveal recurrent attacks with ascites, lasting a few days, and resolving spontaneously, which can be of great help in assessing ultrasound and CT images in an abdominal attack in a patient with C1INH-HAE as well as in qualification to perform these tests.

Considering the above, recurrent ascites during progression and the most acute stage of abdominal pain, which resolves during the attack, may be a specific sign or symptom of an abdominal attack in patients with C1INH-HAE [5, 10, 34–37]. Therefore, when evaluating abdominal ultrasound or CT findings during an abdominal attack in patients with C1INH-HAE or in patients with

a suspicion of acquired C1INH deficiency in the course of other conditions [2–6, 10, 32–35, 37], it is important to remember that the presence and amount of free abdominal fluid is variable and transient. The fluid may be completely absent or present only in small amounts, both in the early stage of the attack and during resolution of abdominal symptoms.

As stated above, when interpreting abdominal imaging findings or referring patients for imaging tests to establish the cause of an abdominal attack in patients with C1INH-HAE, it is especially important and valuable to consider data from medical and family history, physical examination of the patient during an attack, as well as the characteristic presentation of the attack itself. The typical clinical signs and symptoms that can be recognized on the basis of medical history and that fulfil the diagnostic criteria for an abdominal attack in C1INH-HAE include recurrent abdominal attacks lasting several days, often with concomitant vomiting, and resolving gradually and spontaneously within 3 to 5 days. They may be accompanied by localized external swelling or erythema marginatum. The diagnosis is facilitated by a positive family history or confirmed C1INH deficiency in medical records. Medical history may also report the effectiveness of plasma-derived C1INH administered during the attack [5, 22].

The analysis of data from exploratory laparotomies performed during an abdominal attack in a patient with C1INH-HAE may be particularly valuable. In our study, laparotomy was performed in 33% of patients. In 8 cases, no surgical cause of acute abdominal attack apart from ascites and, less frequently, segmental bowel wall thickening was revealed. This confirms that laparotomy is often unnecessary in these patients, as previously reported by other authors [5, 6, 10, 19, 20, 23]. Patients with C1INH-HAE with isolated abdominal attacks constitute an important diagnostic challenge [23, 27–29, 35, 37]. In our study, an abdominal attack was the first, and for some time the only, symptom of HAE in as many as 45% of patients with C1INH-HAE, often children, which is in line with previous reports [5, 6, 14]. Our results as well as available literature data allow us to assume that an abdominal attack in C1INH-HAE may be recognized using ultrasound imaging on the basis of segmental bowel wall thickening as well as significant fluid accumulation, both resolving spontaneously, usually by the end of day 2 of the attack. Ultrasound examination is easily accessible, safe, and quick to perform. On the other hand, abdominal or pelvic CT provides more details that allow clinicians to assess the severity and extent of bowel thickening, examine mesenteric lesions, and evaluate the volume and distribution of free peritoneal fluid. Moreover, it makes it possible to exclude other potential causes of an acute abdominal attack, such as appendicitis, diverticulitis, or gastrointestinal perforation [10, 19, 20, 40]. However, CT examination is not always feasible in patients with C1INH-HAE with acute abdomen, who require prompt management due to a severe clinical condition, as reported previously by numerous other authors [10, 17, 19, 20, 33, 35].

Importantly, if C1INH-HAE is suspected in a patient with an acute abdominal attack, it is necessary to assess C1INH levels and functional activity as well as C4 level. An immediate measurement is not always possible in an acute state, but it allows the final diagnosis to be established. This is important because similar abdominal attacks may also occur (although rarely) in patients with acquired angioedema due to C1INH deficiency in the course of other conditions such as T-cell proliferative disease or autoimmune diseases as well as in response to angiotensin-converting enzyme inhibitors [2, 3].

Conclusions

Abdominal and pelvic ultrasound and CT are valuable diagnostic tools in patients with abdominal attacks in the course of C1INH-HAE, provided that they are performed during symptom progression or highest symptom severity.

Ascites and segmental bowel thickening are the most common self-limited symptoms of abdominal attacks in patients with C1INH-HAE, and they resolve spontaneously or after administration of an appropriate treatment.

Medical history (recurrent abdominal attacks, especially with ascites, confirmed C1INH deficiency, positive family history) and the presence of external swelling as well as erythema marginatum on physical examination during an attack are useful clinical criteria for radiological recognizing an abdominal attack due to C1INH-HAE. They may be used to aid the interpretation of imaging findings or when assessing patient eligibility for imaging tests.

Conflict of interest

The authors declare no conflict of interest.

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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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Podsumowanie badań - materiał i metody:

Do badania włączono 322 chorych (230 kobiet i 102 mężczyzn w wieku 4-70 lat), z rozpoznaniem C1INH-HAE typ 1 i 2 ustalonym na podstawie wywiadu, badania fizykalnego w remisji i napadzie oraz badań laboratoryjnych obejmujących oznaczenie w surowicy poziomu C1 INH oraz C4 i poziomu aktywności C1 INH w plazmie.

Aktywność C1INH była oceniana z zastosowaniem Berichrom C1-inhibitor assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Poziom C1 INH i C4 w surowicy oznaczano metodą nefelo metryczną (Siemens Healthcare Diagnostics, Deerfield, IL, USA)

Analizie retrospektywnej poddano:

a. wywiad obejmujący objawy napadowe obrzęku, ich lokalizację, częstość i przebieg napadów, objawy zwiastujące napad i skuteczność leków oraz wywiad rodzinny
b. laboratoryjne badanie poziomu i aktywności C1INH oraz C4
c. wyniki badań obrazowych (USG/CT) jamy brzusznej oraz miednicy wykonanych u chorych z napadami brzusznymi w okresie ostrych objawów brzusznych i w remisji.

Podsumowanie wyników badań:

Przeprowadzone badania wykazały:

1. Spośród 322 chorych objętych badaniem u 274 chorych (co stanowi 85% badanych (190 kobiet i 84 mężczyzn w wieku 4-70 lat).) wykazano obecność napadów. Częstość napadów brzusznych w tej grupie chorych wahała się od 1 do 15 na rok. U 49% badanych napady brzuszne były pierwszym i czasami przez wiele lat jedynymi objawami choroby. Napady każdorazowo stanowiły problem diagnostyczny warunkujący prawidłowe leczenie.
2. Rozpoznanie ułatwiały:
   a) dodatkowe objawy towarzyszące objawom brzusznym, jak np. rumień brzeżny występujący u 45% badanych, zewnętrzny obrzęk naczynioruchowy towarzyszący napadowi brzusznemu u 30% chorych lub obrzęk krtani obecny u 10% chorych
   b) charakterystyczne cechy i przebieg napadów brzusznych możliwe do analizy na podstawie wywiadu z chorym:
   - 2-5 dniowy przebieg, różna częstość, zwykle trudna nieuchwytna przyczyna

- wielogodzinne narastanie nasilenia bóli czasem o zmiennej lokalizacji zwykle silne wzdęcie, wymioty lub biegunka oraz spontaniczne powolne ustępowanie objawów od 2-3 doby
- w przypadkach z ustalonym rozpoznaniem podanie rekomendowanych leków (C1INH, ikatybant, ecallandyna) do 1-2 godzin powodowało wstrzymanie rozwoju dolegliwości brzusznych i ich ustępowanie w krótkim czasie (do kilku godzin).

c) trudności diagnostyczne u 58 chorych (21%) były przyczyną zwiadowczej laparotomi, która w 48 przypadkach (80%) nie wyjaśniała przyczyny napadu brzusznego, a najczęściej ujawniała jedynie obfitą ilość płynu w jamie brzusznej - w 12 pozostałych przypadkach laparotomia wykazała przyczynę obrazu ostrego brzucha – najczęściej wynik ostrego zapalenia wyrostka robaczkowego

c) analiza badań obrazowych (USG/CT jamy brzusznej i miednicy) wykonanych w okresie narastania objawów brzusznych ujawniała często obecność wolnego płynu w jamie otrzewnej, a także odcinkowy, okrężny obrzęk ściany jelit. Dodatkowo w badaniu CT w/w zmianom często towarzyszył obrzęk węzłów chłonnych krezkowych oraz płyn w świetle jelit. Kontrolne badania wykonane w okresie ustępowania dolegliwości brzusznych lub w okresie pełnej remisji objawów ujawniały całkowite ustępowanie w/w zmian zarówno w samoistnej remisji jak i po zastosowaniu rekomendowanego leczenia farmakologicznego. Jedynie 56 osób z pośród 274 chorych (ok 20%) spośród zebranego retrospektywnie materiału miało wykonane badanie obrazowe w czasie występowania objawów brzusznych.

Wnioski:

1. analiza retrospektywna 322 chorych *(dorosłych i dzieci)* z wrodzonym obrzękiem naczynioruchowym na tle niedoboru C1-INH typu I i II (choroba rzadka) wykazała obecność ostrych nawracających napadów brzusznych u ponad 85% badanych I każdorazowo napady te stanowiły problem diagnostyczny. W 49% przypadków były one pierwszym, czasami jedynym objawem choroby. U 21% chorych były przyczyną niepotrzebnej laparototomii eksploratywnej.

2 analiza badań obrazowych (USG/CT) jamy brzusznej i miednicy wykonywanych podczas napadu brzusznego u chorych z HAE wykazała najczęściej pojawiające się w okresie narastania ostrych objawów brzusznych odcinkowy obrzęk jelit oraz obecność obfitego płynu w jamie otrzewnej, a także ich ustępowania wraz z dolegliwościami – co wskazuje na ich diagnostyczną wartość.

3. wykazano istotną zależność zmian widocznych badan obrazowych z obrazem klinicznym pacjenta w trakcie ostrych objawów brzusznych pozwalającą na monitorowanie i przebiegu napadu brzusznego a także na ocenę skuteczności jego leczenia.

4. wykazano, że w radiologicznej ocenie zmian obrazowych jamy brzusznej i miednicy (zwłaszcza USG) wykonanych w napadzie brzusznym u chorych z C1 INH HAE istotnie pomocne mogą być dane z wywiadu (potwierdzony u chorego niedobór C1 INH, obecność w wywiadzie nawracających kilkudniowych napadów brzusznych, zwłaszcza z samo ustępującym wodobrzuszem) a także obecność widocznego w badaniu fizykalnym towarzyszącego napadom brzusznym obrzęku naczynioruchowy tkanek zewnętrznych lub obecność rumienia brzeżnego.

Streszczenie:

Wrodzony obrzęk naczynioruchowy jest rzadką chorobą genetyczną (1:50 tyś) spowodowaną niedoborem C1 inhibitor (C1-INH - głównego inhibitora produkcji kinin). wskutek różnorodnych mutacji jego genu (SERPING1). Objawy tej choroby (Hereditary angioedema – C1INH-HAE) charakteryzują się nawracającymi napadami 2-5 dniowego ograniczonego obrzęku tkanki podskórnej (najczęściej dłoni, stóp, twarzy) lub podśluzowej np. jelit czy górnych dróg oddechowych o różnej częstości (1–15 i więcej na rok) a także o różnym nasileniu. Obrzęki te są oporne na leczenie glikokortykosterydami (GKS) i lekami przeciwhistaminowymi. Napady obrzęku naczynioruchowego u chorych z tym schorzeniem są indukowane bradykininą (BK), której produkcja jest regulowana w warunkach prawidłowych inhibitorem C1-INH. - głównym inhibitorem generacji kinin.

Szczególnym problemem są napady obrzęku tkanek podśluzowych narządów wewnętrznych. W przypadku zajęcia dróg oddechowych co występuje stosunkowo rzadko stanowią zagrożenie dla życia przez zwężenie światła górnych dróg oddechowych. W przypadku często występujących napadów obrzęków tkanki podśluzówkowej różnych rejonów przewodu pokarmowego są przyczyną ostrych napadów brzusznych wymagających każdorazowo różnicowania z ostrym brzuchem. Prawidłowe rozpoznanie przyczyny napadu brzusznego u chorych z C1-INH-HAE umożliwia właściwe jego leczenie skutecznymi rekomendowanymi lekami oraz pozwala ograniczyć powikłania oraz ilość wykonywanych zwiadowczych zabiegów chirurgicznych.

Celem pracy były:

1. retrospektywna analiza problemów diagnostycznych i leczniczych napadów brzusznych u 274 chorych (dorosłych i dzieci) z wrodzonym obrzękiem naczynioruchowym w przebiegu niedoboru C1-INH typu I i II.

2. ustalenie przydatności badań obrazowych (USG/CT) jamy brzusznej i miednicy w rozwiązywaniu problemów diagnostycznych napadów brzusznych u chorych z wrodzonym obrzękiem naczynioruchowym na tle niedoboru C1 inhibitora – (Hereditary angioedema due to C1inhibitor deficiency).

3. ocena przydatności badań obrazowych badań w monitorowaniu skuteczności leczenia napadu brzusznego u chorych z tym schorzeniem.

4. ustalenie wartości pomocniczej roli w interpretacji zmian stwierdzanych w badaniach obrazowy jamy brzusznej w łączności z wywiadem i z badaniem fizykalnym w rozpoznaniu przyczyn napadowych dolegliwości brzusznych u pacjentów z HAE.

Analizie retrospektywnej poddano 274 chorych (190 kobiet i 84 mężczyzn w wieku średnim 36 lat (4-70)) z rozpoznanym C1-INH-HAE typ 1 i 2 i nawracającymi napadami brzusznymi w jego przebiegu wyłonionych z grupy 322 chorych z tym schorzeniem, co stanowi 84,6% chorych pozostających w stałym leczeniu Centrum HAE Szpitala Uniwersyteckiego w Krakow i potwierdza wysoki odsetek chorych z napadami brzusznymi w przebiegu tego schorzenia. Wyniki badań opracowano i wydano w formie 3 prac (2 oryginalne i 1 kazuistyczna). Wykazano, że w 49% przypadków napady brzuszne były pierwszym objawem choroby, zwłaszcza u dzieci i często przez wiele lat jedynym co było przyczyną wieloletnich opóźnień rozpoznania choroby, jej prawidłowego leczenia, zbędnych laparotomii eksploracyjnych i powikłań.

Cechą charakterystyczną napadów brzusznych u tych chorych było występowanie nawracających 2-5 dniowych napadów bóli brzucha narastających wiele godzin i ustępujących samoistnie stopniowo przez 2-3 dni. Nasilenie i lokalizacja dolegliwości były zmienne, częstość zróżnicowana, a przyczyna często nieuchwytna. Towarzyszyło im silne wzdęcie, nawracający silny kolkowy ból brzucha, wymioty lub biegunki, osłabienie, czasami uczucie suchości i objawy odwodnienia.

Szczegółowa analiza przebiegu napadów pozwoliła wskazać na charakterystyczny ich fazowy przebieg. U części chorych napad poprzedzała faza objawów zwiastujących napad, po której pojawiała się kilkugodzinna (do 12 godzin) faza narastających objawów bólowych, silnego wzdęcia, wymiotów/biegunek, osłabienia. Następnie w przypadkach nieleczonych następował wielogodzinny (zwykle do 24 h) okres objawów szczytowych kończący się spontanicznym stopniowym ich ustępowaniem trwającym 1-2 dni.

Obecność objawów zwiastunowych, pojawiających się zwykle kilka godzin przed napadem ostrych objawów brzusznych wykazano u 45% chorych. Najczęstszym wśród nich rumień brzeżny narastający stopniowo i ustępujący wraz z objawami napadu brzusznego. Do innych należały zmiany nastroju, osłabienie, bóle mięśni, senność. 35% chorych wskazywało na obfity posiłek, stres, infekcje lub znaczny wysiłek fizyczny jako czynniki prowokujące napad. 30% chorych zgłaszało równocześnie występowanie w napadzie brzusznym obrzęków podskórnych zwykle dłoni, stóp lub twarzy.

21% (58 chorych) w napadzie brzusznym miało wykonaną laparotomię zwiadowczą wskutek trudności w ustaleniu przyczyny napadu u 45 chorych (78%) laparotomia nie ujawniła przyczyny napadu, wykazano jedynie obecność wolnego płynu w jamie otrzewnej lub/i odcinkowy obrzęk pętli jelit. W 12 przypadkach laparotomia wykazała przyczynę objawów – w 9 przypadkach było to ostre zapalenie wyrostka robaczkowego oraz w 3 przy-

padkach niedrożności przewodu pokarmowego na wskutek wgłobienia jelita w przebiegu napadu HAE. U 1 chorego stwierdzono perforację bezobjawowego owrzodzenia dwunastnicy w toku przedłużającego się napadu brzusznego HAE.

W objętej analizą grupie chorych diagnostyczne badanie obrazowe jamy brzusznej i miednicy (USG/CT) w napadzie ostrych objawów brzusznych wykonywane było jedynie u 56 chorych (20%) warunkowane stanem chorego i dostępnością do aparatury. U 60% z tej grupy chorych wykazano obecność obfitego płynu w wolnej jamie brzusznej/ miednicy i odcinkowego obrzęku jelita cienkiego. W badaniu CT obserwowano ponadto poszerzenie węzłów kreskowych wzdłuż ściany obrzękłego jelita. Zmiany te były przejściowe, obecne jedynie w okresie ostrych, narastających objawów brzusznych. Ustępowały spontanicznie wraz z objawami, zwykle od drugiej doby napadu wraz z objawami brzusznymi lub do 2 godzin po podaniu rekomendowanych leków (pdC1INH lub icatibant).

Badania obrazowe jamy brzusznej (USG/CT) w zależności od stanu pacjenta i dostępności aparatury są pomocnym, narzędziem diagnostycznym, umożliwiającym diagnostykę i monitorowanie skuteczności leczenia w ostrym napadzie brzusznym u pacjentów w przebiegu HAE, a także na diagnostykę różnicową innych chorób dających objawy ostrego brzucha zmniejszając tym samym ilość mylnych rozpoznań i zbędnych laparotomii zwiadowczych.

Abstract

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare hereditary disease characterized by recurrent subcutaneous or submucosal angioedema due to uncontrolled bradykinin production caused by C1-INH dysfunction. Submucosal gastrointestinal swellings provoking abdominal attacks are common and mimic acute abdomen, thus constituting a diagnostic challenge. We aimed to investigate the difficulties in diagnosing abdominal attacks in patients with C1-INH-HAE and to assess the diagnostic value of medical history, the course of the attack, abdominal imaging, and treatment efficacy. The retrospective analysis of diagnostic problems and treatment complications of abdominal attacks in 274 patients with C1-INH-HAE were performed. The value of history, laboratory findings, prodromal symptoms and course of attacks and imaging were assessed. Abdominal attacks were confirmed in 274 of the 322 patients (85%; 190 women and 84 men; age, 4–70 years). In 49% of cases, the abdominal attack was the first and the only symptom for years. The simultaneous presence of marginal erythema (45% of cases), subcutaneous edema (30%), and pharyngo-laryngeal edema (10%) facilitated the diagnosis of an abdominal attack due to C1-INHHAE. Abdominal attacks manifested with recurrent acute abdominal symptoms lasting 2 to 5 days. The disease course was characterized by the phase of progressive prodromal symptoms followed by peak symptoms and spontaneous symptom resolution. Abdominal imaging often revealed abundant ascites and limited bowel edema. In 60 cases (22%), the diagnostic difficulties resulted in exploratory laparotomy, which was inconclusive in 48 patients (80%). The attacks usually subsided within 2 hours from the administration of recommended drugs (plasma-derived C1-INH , recombinant C1-INH or icatibant). We conclude that recurrent abdominal attacks lasting a few days and resolving spontaneously were common symptoms of C1-INH-HAE. Abdominal imaging revealed transitional fluid or bowel edema. The effectiveness of recommended drugs as plasma-derived C1-INH, recombinant C1-INH or icatibant confirmed the diagnosis

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Jako współautor pracy pt.

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J Physiol Pharmacol 2022 ;73(2): 253-260

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