

Gastrointestinal manifestations of angioedema: a potential area of misdiagnosis

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Abdominal pain is one of the most common conditions leading people to the emergency department. An uncommon but well described cause of abdominal pain is angioedema of the gastrointestinal tract due to recurrent angioedema without wheals. Abdominal involvement is very common in hereditary angioedema (HAE), but it is also described in acquired angioedema and allergic forms. In patients with HAE, the involvement of gastrointestinal tract with resultant abdominal pain occurs in 43–93% of cases. Attacks can involve the entire gastrointestinal tract, such as the oropharynx, small intestine, colon, liver, or pancreas. Pain is the most common gastrointestinal symptom, and it may occur for many years even without cutaneous or respiratory symptoms. The case report we included in this article emphasizes the importance of accurate evaluation of personal and family history in patients with a long history of acute, severe, and unexplained abdominal pain, and it gives an example of how diagnostic delay may be longer if gastroenterological symptoms are the predominant clinical presentation. Furthermore, sometimes the simultaneous presence of concomitant gastrointestinal disorders and HAE may cause difficulties in differential diagnosis. Gastroenterologists and other physicians should add HAE to their list of potential causes of unexplained abdominal pain. The initiation of appropriate prophylaxis and treatment will prevent needless suffering and useless surgical and medical procedures. *Eur J Gastroenterol Hepatol* 33: 787–793
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Introduction

Abdominal pain is one of the most common conditions leading people to the emergency department (ED), accounting for up to 7–10% of all ED visits [1]. It could have a wide number of possible etiologies; for this reason, identifying the underlying causes of pain is often a challenge in clinical practice.

An uncommon but well described cause of abdominal pain is angioedema of the gastrointestinal tract due to recurrent angioedema without wheals [2].

Angioedema is a clinical manifestation characterized by swelling of cutaneous and subcutaneous tissues, due to vascular reactions of deeper layers of skin and mucous membrane with increased blood vessel permeability [3].

The current classification of angioedema without urticaria distinguishes two main forms, hereditary angioedema (HAE) and acquired angioedema (AAE) [4].

The best described form of HAE is the C1 inhibitor deficiency HAE (C1-INH-HAE), which is caused by mutations in the C1 inhibitor gene (*SERPINC1*) and occurs in

quantitative (type I) or functional (type II) C1-INH deficiency [5]. Furthermore, several other forms with normal C1-INH have been described, they can be caused by mutations in other genes such as *factor 12* (FXII-HAE), *plasminogen* (PLG-HAE), *angiopoietin-1* (ANGPT1-HAE), and *kininogen-1* (KNG1-HAE) [5–7]. In other HAE with normal C1-INH families, the genetic background is still unknown.

Four types of AAE are described as separate entities [6]. The most frequent form of AAE is induced by drugs, and angiotensin-converting enzyme (ACE) inhibitors are the most commonly involved medications (ACEI-AAE) [8]. Acquired C1-INH deficiency (C1-INH-AAE) is a rare condition in which the reduction of C1-INH is often linked to autoimmune or lymphoproliferative diseases [9]. In a large group of patients, the cause of recurrent angioedema remains unclear (idiopathic angioedema); therefore, these forms are classified as histaminergic (IH-AAE) or non-histaminergic (InH-AAE) based on the improvement of symptoms in response to continuous treatment with antihistamines.

The clinical spectrum of the angioedema attacks differs among the different types of angioedema, depending on the underlying pathogenetic mechanism. For example, ACEI-AAE typically affects the tongue and high airways [10], while C1-INH-AAE mainly affects the face, upper respiratory tract, and abdomen [9].

The clinical features of HAE and AAE with normal C1-INH are very similar to each other and to that with C1-INH deficiency. However, the gastrointestinal involvement seems to be more common in HAE. Indeed, in a survey of 94 patients with HAE or AAE with normal C1-INH, the only difference in clinical presentation was the presence of abdominal symptoms, which was higher

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in HAE [11]. Therefore, gastrointestinal involvement is very common in HAE, but it is also described in C1-INH-AAE, ACEI-AAE, nonsteroidal anti-inflammatory drugs (NSAIDs)-induced angioedema, allergic angioedema, and idiopathic angioedema [12]. Anyway, although some features can guide the diagnosis, the clinical heterogeneity, which is not always predictable, can lead to a diagnostic delay and affect the therapeutic management. Also, a great variability is often observed among patients affected by the same angioedema type and even in the same patient in different stages of life.

However, gastrointestinal involvement represents up to 80% of clinical presentation in HAE [13]; interestingly isolated abdominal symptoms, without visible signs of cutaneous swelling, may occur in up to 21% of C1-INH-HAE patients [14], in such a case, the evaluating clinician may not consider HAE in differential diagnosis. Indeed, the gastrointestinal involvement in HAE may present with signs and symptoms which are often nonspecific and that may resemble those of more common gastrointestinal conditions. Furthermore, the simultaneous occurrence of other gastroenterological clinical entities in the same patient may cause additional difficulties because of the overlapping nature of their manifestations. The presence in the same patient of both gastrointestinal disease (e.g., celiac disease, Chron's disease, and ulcerative colitis) and HAE has occasionally been reported (Table 1), but it is unclear if a pathogenetic link exists between immune-mediated gastrointestinal disease and HAE. These patients may be particularly challenging for physicians, as the symptoms complained of could be referred to the underlying gastrointestinal disorder. Hence, an unexplained worsening of symptoms in terms of severity and frequency, as well as an ineffective response to therapy justifies additional diagnostic workup for ruling out concomitant disorders, possibly including rare diseases such as HAE.

Dealing with the possibility of HAE and concomitant gastrointestinal disorders, a separate mention should be made to the relationship between *Helicobacter pylori* infection and C1-INH-HAE. Indeed, it has been reported that *H. pylori* infection seems to increase the frequency of abdominal symptoms [17,18], and that the frequency of attacks may decrease substantially following the eradication of this pathogen [18].

Gastroenterologists are the most likely of all physician specialties to encounter patients with recurrent episodes of abdominal pain for any cause; therefore, they should raise awareness about uncommon causes of

abdominal pain. A correct clinical assessment, laboratory testing, and appropriate differential diagnosis allow the initiation of the appropriate treatment, because misdiagnosis and diagnostic delay have a strong impact on clinical outcomes and health-related quality of life of HAE patients [25].

Gastrointestinal manifestations of hereditary angioedema

In patients with HAE, the involvement of gastrointestinal tract with resultant abdominal pain occurs in 43–93% of cases. The attacks can involve the entire gastrointestinal tract, such as the oropharynx, small intestine, colon, liver, or pancreas [2].

The pain is the most common gastrointestinal symptom of HAE abdominal attacks, and it is often described as a cramping or colicky recurrent pain of variable severity [13]. The abdominal pain symptoms may occur for many years even without cutaneous or respiratory symptoms [2]. Also, pain may manifest as acute onset due to the partial or complete intestinal obstruction and it may mimic an abdominal catastrophe. In these cases, misdiagnosis can lead to unnecessary surgical procedures. According to Agostoni *et al.* [26], out of 235 patients with hereditary or acquired C1-INH deficiency experiencing abdominal symptoms, 1/3 underwent appendectomies or exploratory laparotomies.

Patients affected by HAE may also experience nausea and vomiting, which occur in 78% of patients, while diarrhea manifests in 65% of patients. In addition, the attacks may involve the oropharynx and esophagus, resulting in dysphagia, or the colon, causing constipation [2].

Abdominal HAE attacks may be preceded by prodromal symptoms such as fatigue, irritability, hunger, and erythema marginatum.

Furthermore, unusual gastrointestinal presentations of HAE are possible, and they represent a potential area of misdiagnosis and a challenge in clinical practice (Table 2). For example, hepatic and pancreatic localizations are very rare but possible. The latter has been described by Cutler *et al.* [36] reporting a patient with recurrent episodes of abdominal pain and elevation in amylase and lipase, which were contemporary to cutaneous swelling. After the exclusion of other causes of pancreatitis, they postulated that an intermittent intrapancreatic edema could induce partial ductal obstruction with resultant pancreatitis, or, alternatively, the loss of inhibition of the

Table 1. Association between gastrointestinal disorders and hereditary angioedema

References	HAE patients described (Number)	HAE patients with concomitant gastrointestinal disorders (%)	Gastrointestinal disorder
Farkas <i>et al.</i> [15]	1	100% (1/1)	Crohn's disease
Rais <i>et al.</i> [16]	1	100% (1/1)	<i>Helicobacter pylori</i> infection
Farkas <i>et al.</i> [17]	65	29.2% (19/65)	<i>Helicobacter pylori</i> infection
Visy <i>et al.</i> [18]	152	43.9% (61/152)	<i>Helicobacter pylori</i> infection
Farkas <i>et al.</i> [19]	1	100% (1/1)	Celiac disease
Williams <i>et al.</i> [20]	1	100% (1/1)	Celiac disease
Csuka <i>et al.</i> [21]	129	3.1% (4/129)	Celiac disease
Farkas <i>et al.</i> [22]	130	3% (4/130)	Celiac disease
		0.76% (1/130)	Crohn's disease
Kessel <i>et al.</i> [23]	61	3.2% (2/61)	Celiac disease
		1.6% (1/61)	Crohn's disease
Desai <i>et al.</i> [24]	1	100% (1/1)	Ulcerative colitis

HAE, hereditary angioedema.

Table 2. Unusual gastrointestinal presentation of hereditary angioedema as potential area of misdiagnosis

References	Clinical manifestations	Frequency
Farkas <i>et al.</i> [27]	Ascites	80%
Gabos <i>et al.</i> [28]	Ascites	Case report
Cohen <i>et al.</i> [29]	Hypovolemic shock	Case report
Bork <i>et al.</i> [30]	Hypovolemic shock	4.4%
Wu <i>et al.</i> [31]	Retroperitoneal angioedema	Rare
Witschi <i>et al.</i> [32]	Intussusception	Rare
Patel <i>et al.</i> [13]	Intussusception	Case report
Figuerola-Diaz <i>et al.</i> [33]	Intussusception	Case report
Cheng <i>et al.</i> [34]	Intussusception	0.05%
Farkas <i>et al.</i> [35]	Elevated transaminase levels; Hepatic parenchymal changes	Rare
Cutler <i>et al.</i> [36]	Pancreatitis	Case report
Matesic <i>et al.</i> [37]	Pancreatitis	Case report
Cancian <i>et al.</i> [38]	Pancreatitis	Case report
Czaller <i>et al.</i> [39]	Pancreatitis	Case report
Berger <i>et al.</i> [40]	Pancreatitis	Case report
Aksoy <i>et al.</i> [41]	Pancreatitis	Case report
Lopes Veronez <i>et al.</i> [42]	Pancreatitis	Case report

kallikrein–kinin system in HAE could produce an excess of kinins, which are known to be implicated in the pathogenesis of pancreatitis [36]. Also, Lopes-Veronez *et al.* [42] report three patients with acute pancreatitis, two of them diagnosed with C1-INH-HAE and one patient with FXII-HAE. Interestingly, in HAE-related pancreatitis, the specific treatments [e.g., plasma-derived C1 esterase inhibitor concentrate (pdhC1INH) and icatibant] seems to promptly induce a relief of symptoms, normalization of amylase, and resolution of pancreatitis within 24–72 h [38,39,42,43].

Hepatic involvement manifests with elevation in transaminases, ascites, and reversible parenchymal changes [13]. Ascites can be due to gastrointestinal tract edema, and it may be an indicator of the severity of an attack [27]. Ascites observed in these patients is exudative, transient and usually disappears in 48–72 h after the first symptoms. Concurrently to an abdominal HAE attack, the patients may develop hypovolemic shock with associated hemoconcentration if the ascites and bowel edema are severe. Also, in some cases, ascites has been described associated with leukocytosis and low-grade fever.

Diagnosis of C1-INH-HAE must be ruled out by executing the C1-INH level, C1-INH activity, and by the measurement of complement components (C4 and C1q). C1-INH gene testing is not mandatory, but it should be performed to confirm the diagnosis in the case of uncertainty and for C1-INH-HAE screening in patients less than 1 year of age [44]. Mutations in *SERPINC1* can be identified in 95% of cases [45]. Otherwise, genetic testing is always required in the suspicion of HAE with normal C1-INH [6]. Hence, the diagnosis of HAE cannot be determined through radiologic tests in patients with gastrointestinal attacks; however, these investigations may be useful in excluding all other causes of abdominal pain. A commonly executed test in emergency setting is abdominal ultrasound, which can identify ascites and bowel edema [13]. Abdominal radiographs show ‘thumbprinting’, which describes areas of mucosal edema. A computed tomography (CT) scan of the abdomen is useful to identify also milder alterations.

Endoscopic descriptions of HAE have been reported incidentally during undiagnosed HAE attacks as diffuse mucosal edema and erythema and bulging areas of gastric

mucosa in upper endoscopy, or as edematous colonic mucosa without pronounced signs of inflammation in colonoscopy [14]. Stomach mucosal biopsies during attacks of HAE show moderate nonspecific inflammatory cell infiltration and edema of the lamina propria [46].

However, endoscopy is not needed for diagnosis. Furthermore, in patients known to or suspected to have HAE, endoscopic procedures may become a trigger for severe or even potentially life-threatening attacks. If endoscopy is compelling, prophylactic measures against laryngeal swelling should be undertaken [short-term prophylaxis (STP) before the procedure and availability of pdhC1INH during the procedure] [2,3,13].

Case report

A 21-year-old white woman presented at our Center (Campania Referral Center for Recurrent Angioedema, University of Naples Federico II, Naples, Italy) to undergo allergic workup due to suspected drug allergy to ampicillin (urticaria).

Her past medical history was significant for recurrent gastroenterological symptoms such as abdominal pain, distension, and diarrhea she had experienced since her childhood. Given that symptoms were accompanied by growth retardation, the patient was admitted to the hospital for the first time at the age of 9, where she underwent upper gastrointestinal endoscopy with biopsy. The histological pattern was compatible with celiac disease. She was also tested for HLA-DQ2 and IgA anti-transglutaminase, both resulted positive. She started gluten-free diet with initial clinical and histological improvement. By the age of 12, despite compliance to the gluten-free diet, she started to complain a recurrence of colic abdominal pain and the appearance of a new symptomatology with transient episodes of edema of the skin with no urticaria or itch associated, laryngeal edema, dysphonia, and dyspnea. The frequency of these attacks was at least once-weekly, sometimes correlated to her period, and was not responsive to steroid therapy. At the age of 16, the patient presented to the ED with nonbloody and nonbilious emesis and acute right lower quadrant abdominal pain. Hence, given the presumed diagnosis of acute appendicitis, she underwent an appendectomy.

The patient's mother also had similar recurrent abdominal aches and skin swelling and her maternal grandfather died of dyspnea of unknown origin. Given personal and family history, she performed dosage of C1-INH antigen (undetectable), C4 (0.035 g/L; normal 0.1–0.4) and C1-INH activity assay (11%; normal >50); the genetical examination showed c.2T>C (p.M-22T) mutation in *SERPING1* [47]. Laboratory and genetic tests were performed also in patient's mother and children. She was diagnosed of C1-INH-HAE type I, same as her mother and two of her three children.

She started a long-term prophylaxis (LTP) with tranexamic acid (TXA), pdhC1INH at a dose of 20 U/kg was prescribed for the treatment of the acute attacks. The efficacy of TXA resulted unsatisfactory; therefore, due to the high frequency of attacks, she switched to danazol 100 mg/die, with no improvement of symptoms after 2 years. Then, LTP with pdhC1INH at a dose of 1000 UI every 4 days was prescribed, with a complete resolution of the symptomatology and no attacks in the last 4 years.

Discussion

Due to its rarity and heterogeneity of manifestations, C1-INH-HAE is often poorly recognized, resulting in misdiagnoses and diagnostic delay, inadequate treatment, and unnecessary procedures, putting patients at an increased risk of morbidity and mortality [48].

Indeed, abdominal attacks may be confused with the clinical presentation of more common gastrointestinal disorders such as appendicitis, cholecystitis, pancreatitis, celiac disease, food allergy, ischemic, and inflammatory bowel disease.

This report emphasizes the importance of accurately evaluating personal and family anamnesis in patients with a long history of acute, severe, and medically unexplained abdominal pain. The patient we described was diagnosed after 12 years from the beginning of symptoms, despite her mother suffered the same symptoms and her grandfather died of dyspnea of unknown origin. Because C1-INH-HAE is an autosomal dominant hereditary disease, among patient's relatives genetic testing could be used to find out the diagnosis of C1-INH-HAE even before the onset of symptoms. For this reason, patient's children underwent genetical investigation and two of them received an early diagnosis of C1-INH-HAE. This strategy will be helpful planning a tailored and effective management of the disease including a correct primary prevention of the attacks. Indeed, C1-INH-HAE attacks are often triggered by some factors such as infections, emotional stress, physical exertion, trauma, invasive medical procedures, and menstruation, as well as treatment with certain medications (i.e., ACEIs and contraceptive) [6]. Also, in recent studies, food ingestion has been suggested as a trigger for abdominal attacks [49,50]. On the other hand, there have been a few case reports of C1-INH-HAE resembling food allergy, considering that C1-INH-HAE clinical features may resemble those of anaphylactic shock [20,51]. Mechanisms of how foods can trigger attacks have not yet been completely elucidated. IgE-mediated hypersensitivity with mast cell activation can be associated with heparin release and consequent bradykinin generation [52,53] but probably in this case, the reason is not IgE-mediated hypersensitivity,

but rather an intolerance reaction to foods products [50]. Indeed, interestingly in all subjects reported by Steiner *et al.* [50] to mention foods as a trigger factor for abdominal attacks, specific IgE against the indicated food products could not be documented, neither by SPT nor by serological tests. Furthermore, most of the food indicated by the investigated subjects such as cheese, alcoholic beverages, fish, tomatoes, strawberries, pineapples, nuts, citrus fruits, and kiwis contain or release histamine [54]. Therefore, a histamine intolerance reaction is more probably associated with the induction of the attacks.

Also, the concomitance of some gastrointestinal disorders could influence disease severity in C1-INH-HAE patients. Indeed, the *H. pylori* infection has been suggested as a triggering factor of abdominal attacks, given that the frequency of acute abdominal pain in C1-INH-HAE patients is significantly higher in patients infected by this pathogen [17,18]. The pathogenetic mechanism is still unknown, but Visy *et al.* [18] postulated that exacerbations of the attacks might be triggered by activation of humoral immune responses against *H. pylori*, leading to the depletion of C1-INH. This process might result in the uncontrolled activation of complement and other plasma enzyme systems. Also, direct local mucosa damage due to cell death can generate activation of complement and other contact systems. Therefore, screening of patients with C1-INH-HAE for *H. pylori* infection seems warranted, because eradication of this pathogen can lead to a marked reduction in disease severity [18].

Therefore, a proportion of attacks can be prevented through appropriate counseling and changes to lifestyle as the elimination of potential triggering factors is a cornerstone of treatment for HAE [55]. For instance, the patient we reported underwent endoscopic procedures without prophylactic measures against laryngeal swelling, because her condition was not diagnosed yet. Farkas *et al.* [56] confronted two groups of patients with C1-INH-HAE, before and after the diagnosis, and found a significant reduction in the number of postprocedural edematous episodes in the latter when they underwent STP before some procedures (including invasive dental or medical procedures, both operative and diagnostic), with pdhC1-INH concentrate being the most effective drug compared to danazol or TXA. This underscores the importance of diagnosing the condition of HAE: several studies demonstrated an increased mortality in undiagnosed rather than diagnosed HAE patients, essentially due to fatal laryngeal asphyxiation [57,58]. Procedures in undiagnosed patients, performed without STP, may trigger a life-threatening attack, so it is important to build an increased and widespread awareness of this condition.

Moreover, the patient underwent an appendectomy after a severe episode of abdominal pain with vomiting. Appendicitis is one of the most common misdiagnoses received by HAE patients (see below), indeed HAE abdominal attacks may manifest as an acute onset due to the partial or complete intestinal obstruction and they may mimic an abdominal catastrophe. In these cases, misdiagnosis may lead to unnecessary appendectomies or exploratory laparotomies [26], given that gastrointestinal manifestation of HAE is usually transient and they quickly resolve after administration of targeted medical therapy. On the other hand, despite the commonly self-limiting nature and

the good response to medical therapy of the attacks, a persistent abdominal pain after therapy administration may be an alerting feature suggestive of unusual complications eventually requiring surgical intervention. Witschi *et al.* [32] described a case of a young man with a history of C1-INH-HAE presented with protracted abdominal pain which did not reverse with C1-INH infusion. Evaluation by CT scan revealed extensive colorectal intussusception requiring surgical intervention. The intraoperative examination suggested the initiation of intussusception by local mucosal edema in the transverse colon [32]. Anyway, if surgical interventions are needed, a perioperative management plan and multispecialty collaboration for patients undergoing surgery can reduce the likelihood of patient experiencing postoperative HAE attacks or premature mortality. Indeed, the risk of perioperative angioedema in patients with C1-INH-HAE type I or II without prophylaxis undergoing surgical procedures ranged from 5.7 to 30.5% [confidence interval (CI) 3.5–35.7%] [59]. The unpredictability of HAE episodes supports current international treatment recommendations to consider STP before the procedure and availability of pdhC1INH during the procedure for all HAE patients undergoing surgery.

This case report also shows an example of how diagnostic delay may be longer if gastroenterological symptoms are the predominant clinical presentation. Several studies have already tried to deal with this subject and to explore the risk factors associated with a longer diagnostic delay.

A Chinese internet-based survey enrolled 96 patients with C1-INH-HAE, and diagnostic delay was divided into two subperiods, diagnostic delay ≤ 6 years and diagnostic delay > 6 years according to the lower quartile. The median diagnostic delay of all patients was 11.04 years (IQR 6.06–18.27 years). Seventy-five percent of patients reported receiving more than one previous misdiagnosis, and patients with at least a previous misdiagnosis experienced a longer median delay (13.17 years) compared with patients with no previous misdiagnosis (6.96 years). The most common misdiagnoses received included acute gastroenteritis, allergy (unspecified), urticaria, and acute appendicitis. Interestingly, a higher percentage of gastrointestinal edema was detected in patients with diagnostic delay > 6 years (83.3%); those who ever experienced gastrointestinal edema had longer diagnostic delay compared with patients without gastrointestinal edema (13.17 years, range 7.40–20.50 vs 6.79 years, range 3.56–13.35, $P = 0.013$). A younger age of onset and an earlier decade of onset has been reported as predictor of a diagnostic delay > 6 years, while gastrointestinal edema did not reach statistical significance (odds ratio yes vs no 3.06, 95% CI 0.56–16.63, $P = 0.196$) [60].

This study also underlines that C1-INH-HAE patients often see a broad variety of physicians before confirming the diagnosis of C1-INH-HAE: the patients were reported visiting median four hospitals and median six physicians before confirming the diagnosis of C1-INH-HAE. The medical departments most frequently visited were emergency department (90.6%), dermatology (71.9%), allergy (61.5%), gastroenterology (52.1%), rheumatology (34.4%), and otolaryngology (34.4%) [60]. For this reason, it is important to raise awareness of this rare disease among healthcare professionals, because the signs and

symptoms of C1-INH-HAE may resemble those of more common conditions.

An interesting paper evaluated misdiagnosis in patients participating in the Icatibant Outcome Survey (IOS), an observational study in which safety and effectiveness of icatibant have been evaluated since 2009 [61]. In January 2016, 418 of 633 IOS patients with C1-INH-HAE had provided misdiagnosis data, 185 of 418 (44.3%) received one or more prior misdiagnosis, and the most misdiagnoses were allergic angioedema (55.7%) and appendicitis (27%), other misdiagnoses including a substantial number of other gastrointestinal disorders. This range of gastrointestinal misdiagnoses reflects that C1-INH-HAE that affects viscera or bowels may present with abdominal pain and is not necessarily associated with visible swelling. Patients with a prior misdiagnosis confirmed to have a longer median delay to C1-INH-HAE diagnosis than patients without (13.3 vs 1.7 years, $P < 0.001$). Patients with family history of C1-INH-HAE were instead significantly less likely to be misdiagnosed (140 of 336, 41.6% vs 38 of 58, 65.5%, $P < 0.001$).

Last, we report an interesting clinical case described by Valeriewa *et al.* [62] about a 72-year-old man who suffered recurrent abdominal colic-like pain since the age of 8, in which infrequent subcutaneous swellings were attributed to unknown allergic reactions not related to his primary diagnosis of abdominal pain. C1-INH-HAE was diagnosed at the age of 70, after 62 years of diagnostic delay, despite a family history positive for recurrent abdominal pain and skin edema ignored through decades by a large number of physicians, and after the patients underwent three unnecessary surgical interventions and five endoscopies [62].

Furthermore, sometimes the simultaneous presence of concomitant gastrointestinal disorders and HAE may cause difficulties in differential diagnosis. The presence of both gastrointestinal disorders and HAE has occasionally been reported, but only a few studies have been conducted to figure out the possible link between HAE and autoimmune disease.

In HAE, the reduction of the complement components could affect the immune-regulation and the immune-complexes clearance, resulting in inflammatory damage and release of autoantigens, and that in turn may predispose these patients to autoimmunity [63].

However, so far studies have rendered conflicting results. Farkas *et al.* [22] assessed the prevalence of autoimmune disease in general among C1-INH-HAE patients and controls with angioedema not related to complement deficiency, founding no higher prevalence of immunoregulatory disorders among the first group.

Conversely, Brickman *et al.* [64,65] found that there is an increased incidence of autoimmune disorders among C1-INH-HAE patients, and among these conditions, also celiac disease. To date, only a few case reports of concomitant celiac disease and HAE have been published, and it is not clear whether a screening for celiac disease in HAE patients is worth the effort. Csuka *et al.* [21] in a Hungarian study found a significantly higher prevalence of celiac disease in a cohort of 129 C1-INH-HAE patients compared to healthy population (3.1 vs 0.64%, $P < 0.0001$), although these results should be interpreted with caution because of the limited number of screened patients.

It is conceivable that the enhanced capillary permeability which characterizes HAE during attacks, causing edema of the intestinal wall, further increase mucosal permeability in celiac disease, hence opening of intercellular tight junction, enhanced penetration of gliadin fragments into the submucosa, and ultimately the formation of celiac disease autoantibodies (against gliadin, endomysium, and transglutaminase). Although not confirmed, this hypothesis may explain the higher frequency of clinical celiac disease among C1-INH-HAE patients [21].

Mostly, symptoms accompanying HAE episodes are severe and could mimic acute abdominal catastrophe, helping in differential diagnosis since celiac disease symptoms are usually chronic; some patients may experience only mild-to-moderate abdominal pain resembling the celiac disease symptoms.

The efficacy of TXA for LTP in C1-INH-HAE could be unsatisfactory in patients with concomitant celiac disease because some of the products containing TXA (e.g., Exacyl, Sanofi) contains also wheat starch as an inactive ingredient, which is contaminated by gluten, and probably the continuous exposition to gluten may aggravate the gastrointestinal manifestation of celiac disease [21]. In this case, switching to a different drug could be an appropriate therapeutic alternative.

Conclusion

Gastroenterologists and other physicians should add HAE to their list of potential causes of unexplained abdominal pain. The initiation of appropriate prophylaxis and treatment will prevent needless suffering and useless surgical and medical procedures.

It is suggested that complement testing for HAE should be performed in those diagnosed celiac patients in which abdominal symptoms are persisting despite gluten-free diet and histological remission of the gluten-sensitive enteropathy. Conversely, HAE patients unresponsive to adequate therapy should undergo a gastrointestinal workup [19].

The rarity of the above-mentioned conditions does not allow more accurate estimations, but those data suggest the need for more studies about HAE and autoimmune disease (such as celiac disease) correlation.

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Conflicts of interest

There are no conflicts of interest.

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