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An Essential Problem in Patients with Hereditary Angioedema: Irritable Bowel Syndrome

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Abstract

Objective

Hereditary angioedema (HAE) is characterized by attacks of subcutaneous and mucosal edema. HAE usually affects the skin or mucosal tissues of the upper respiratory and gastrointestinal tract. Irritable bowel syndrome (IBS) is one of the diseases in which the abdominal symptoms of HAE may be confused. In this study, we aimed to clarify the role of IBS in clinical presentation and diagnostic delay in HAE.

Material and Method

50 patients with HAE followed in our clinic between January 2013 and April 2023 were included in this study, and hospital records were retrospectively reviewed. Patients with HAE were divided into two groups, those with and without IBS, and evaluated according to Rome IV criteria for diagnosing IBS.

Results

The mean age of the study group was 40 ± 13 years, and 60% (n=30) were female. IBS was observed in 30% (n=15) of the patients, and 60% (n=9) had IBS before diagnosing HAE. The frequency of attacks and history of gastrointestinal tract medical/surgical history were more frequent in HAE patients with IBS (p<0.001, p=0.032, respectively). Abdominal symptoms before the diagnosis of HAE and persistent abdominal symptoms other than attacks after the diagnosis of HAE were more common in HAE patients with IBS (p<0.001, p<0.001, respectively). HAE patients with IBS had a more significant delay in diagnosing HAE (p=0.011).

Conclusion

Clinicians should keep HAE in mind in patients with suspected IBS or patients presenting with recurrent unexplained abdominal pain.

Keywords: Hereditary angioedema, irritable bowel syndrome, abdominal symptoms, frequent attacks, diagnostic delay.

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Introduction

Hereditary angioedema (HAE) is a rare and potentially life-threatening disease that is characterized by itchy swelling of the subcutaneous or submucosal tissues of the skin, extremities, genital organs, and the respiratory and gastrointestinal tracts (1,2). The prevalence of HAE is estimated to be between 1:50000 and 1:100000 (3). HAE can be divided into three types according to the C1 inhibitor (C1-INH) levels and function. Approximately 85% of the HAE cases are caused by C1-INH deficiency (HAE type I), and 15% are caused by C1-INH dysfunction (HAE type II). Patients with HAE who have normal C1-INH levels and function are said to have “HAE with normal C1-INH”(4). Several genetic mutations have been identified in patients with HAE, including mutations in the genes of Factor XII, angiopoietin-1, plasminogen, and kininogen-1 (5). Since HAE is an autosomal dominant disease, patients have a family history of angioedema. However, a family history may not always be present; approximately 25% of HAE cases are caused by de novo mutations (6). Irritable bowel syndrome (IBS) is one of the most common causes of abdominal pain (7). HAE is a rare cause of abdominal pain and can sometimes be misdiagnosed as IBS (8). Therefore, patients with suspected IBS need to be analyzed more thoroughly to prevent a delay in diagnosis and avoid confusion with episodes of HAE-associated abdominal pain. The relationship between HAE and IBS remains unclear. Thus, in this study, we aimed to determine the role of IBS in the clinical presentation and diagnostic delay of HAE.

Material and Method

Study design

This retrospective cohort study was conducted at the Necmettin Erbakan University. The ethics committee approved the study (No: 2023/4368; date of approval). To clinically diagnose IBS, any underlying organic disease should be excluded and the diagnostic criteria should be fulfilled. Data from patients who met the inclusion criteria (age ≥ 18 years and diagnosis of HAE) between January 2013 and April 2023 were collected from their medical records in the hospital database. Complete blood count, erythrocyte sedimentation rate, and stool examination for occult blood, leukocytes, and parasites (examined in three independently collected stool samples) were examined to exclude organic diseases. Again, gastrointestinal system endoscopy and abdominal ultrasonography were performed to exclude organic conditions. Patients with no pathological findings were included in the study. Patients with an underlying organic pathology, such as inflammatory bowel disease, colon cancer, and alarm symptoms, were excluded (Figure 1).

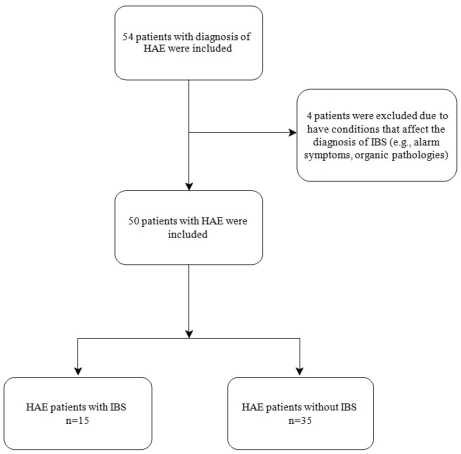

Figure 1:
Flow chart of the inclusion of the study population.
Abbreviations: HAE, hereditary angioedema; IBS, irritable bowel syndrome.

Data Collection

Patient data were obtained from their paper and electronic medical records. The diagnosis of IBS was confirmed using the Rome IV criterion that includes questions regarding the gastrointestinal tract symptoms. Patients with recurrent abdominal pain for an average of at least one day a week over the last 3 months and two or more of the following symptoms were diagnosed with IBS: Change in frequency of defecation, relief with defecation, and change in the stool form (9).

Statistical Analysis

Study data were analyzed with SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA). We used the independent samples T-test to evaluate the continuous data. The chi-square ($\chi 2$) and Fisher’s exact tests were used to evaluate the categorical data. The continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR) and the categorical variables as numbers with percentages. $P < 0.05$ was statistically significant.

Results

Demographic Characteristics of the Patients with HAE

A total of 50 patients with HAE were included in the study. The mean age was 40 ± 13 years, and 60% (n = 30) of the patients were female. Type 1 HAE was present in 56% of the patients and type 2 HAE in 44%. The mean age at which HAE was diagnosed was 30

± 12 years, and the mean delay in making a correct diagnosis was 12 ± 10 years (Table 1). The patients with HAE were divided into two groups: those with IBS and those without. Patients with HAE who had IBS were predominantly female (73.3%), and the mean age was 43.4 ± 11 years. There was no significant difference in age and sex between the two groups (p = 0.259, p = 0.208, respectively) (Table 2).

Frequency of Abdominal Attacks and the Symptom Types

The median number of monthly attacks was 1 (IQR, 1–4), and the attacks were frequent in 28% of the patients. HAE-associated abdominal attacks were seen in 56% of the patients. The primary symptoms of the abdominal attacks were abdominal pain (72%), distension (64%), and nausea (60%). Diarrhoea (14%) and vomiting (20%) were not the predominant symptoms (Table 1).

Gastrointestinal System Findings Other Than an Abdominal Attack

IBS was observed in 30% of the patients, and IBS had been diagnosed before HAE in nine (60%) of the 15 patients with IBS. A medical/surgical history of the gastrointestinal tract was detected in 46% of the patients. A medical/surgical history related to the gastrointestinal tract and frequent attacks were more common in those with IBS than in those without IBS (p < 0.001, p = 0.032, respectively). Furthermore, those with IBS had more gastrointestinal symptoms before the diagnosis of HAE and persistent gastrointestinal symptoms other than abdominal pain after the diagnosis of HAE (p < 0.001, p < 0.001, respectively) (Table 2).

Diagnostic Delay and Misdiagnosis

There was a more significant delay in HAE diagnosis in those with IBS than in those without IBS (p = 0.011).

Symptoms Associated with IBS

Abdominal pain (n = 12) and distension (n = 9) were the most common symptoms of IBS encountered (Figure 2).

Table 1 Patients demographics and the characteristics of hereditary angioedema attacks.

Characteristics	Value
Age (years), mean ± SD	40 ± 13
Sex, n (%)	
Female	30 (60)
Male	20 (40)
Type, n (%)	
I	28 (56)
II	22 (44)
Diagnostic age (years), mean ± SD	30 ± 12
Diagnostic delay (years), mean ± SD	12 ± 10
Number of attacks (per month), median, IQR	1 (1–4)
Frequent attacks, n (%)	14 (28)
Abdominal attacks, n (%)	28 (56)
Abdominal pain	36 (72)
Distension	32 (64)
Nausea	30 (60)
Diarrhea	7 (14)
Vomiting	10 (20)

Abbreviations:IQR, interquartile range; SD, standard deviation.

Table 2 Gastrointestinal system findings other than abdominal attacks.

Variable	Patients with HAE and IBS	Patients with HAE and without IBS	P*
Total, n (%)	15 (30)	35 (70)	
Age (years), mean ± SD	43.4 ± 11	39.1 ± 14.8	0.259
Sex, n (%)			0.208
Female	11 (73.3)	19 (54.3)	
Male	4 (26.7)	16 (45.7)	
Gastrointestinal tract-related medical/surgical history	14 (61)	9 (39)	**<0.001**
Frequent attacks	9 (64)	5 (36)	**0.030**
Gastrointestinal tract symptoms before the diagnosis of HAE	18 (60)	12 (40)	**<0.001**
Persistent gastrointestinal tract symptoms other than attacks after the diagnosis of HAE	17 (61)	11 (39)	**<0.001**
**** Delay in diagnosing HAE, (years)**	18 ± 7.3	10.3 ± 8	**0.011**

* Chi Square test (data were shown as number and percentages).
** Independent samples T-test (data are shown as mean with standard deviation).
Abbreviations: HAE, hereditary angioedema; IBS, irritable bowel syndrome; SD, standard deviation

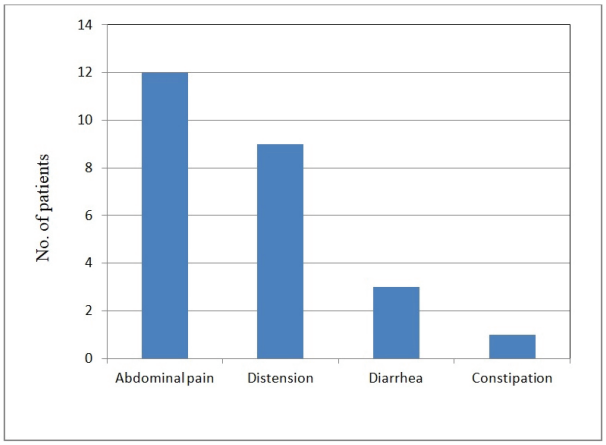

Figure 2:
Symptoms of IBS in patients with hereditary angioedema.

Discussion

Abdominal symptoms are characteristic of HAE. We determined that the most common symptom of patients with HAE was abdominal pain, and 56% of them presented with abdominal attacks. A gastrointestinal tract-related medical/surgical history, frequent attacks, and delay in HAE diagnosis were more common in patients with HAE and IBS. Additionally, the most common symptom encountered in patients with HAE and IBS was abdominal pain.

Abdominal symptoms are the most common findings after diffuse skin edema, especially of the extremities, in HAE. The lips, tongue, eyelids, and genitals may also be affected (10). Similarly, abdominal attacks were observed in most of our study patients. HAE can present with cramping abdominal pain, nausea, or vomiting. The abdominal pain can be severe and acute or recurrent, chronic, or of moderate severity (11). In a previous study, abdominal pain was the most common symptom during abdominal attacks (12). In another study, distension and crampy abdominal pain were the most common symptoms during an abdominal attack (13). Similarly, in this study, abdominal pain and distension were the most common symptoms during abdominal attacks. Diagnosing HAE is usually difficult if there are no skin symptoms; approximately 49% of the patients present with only abdominal pain(13). Abdominal symptoms may precede the skin manifestation for several years; such patients are more likely to be referred to another physician(14). Similar to this study, in a previous study, approximately 70% of patients with HAE had abdominal symptoms, and the mean delay between the onset of symptoms and

diagnosis was 14 years (12). An overlooked cause of abdominal pain is HAE (15). IBS is one of the diseases in which the HAE-related abdominal symptoms are associated with an alternative diagnosis, such as acute abdominal pain, appendicitis, pancreatitis, biliary colic, cholecystitis, nephrolithiasis, choledocholithiasis, and pyelonephritis (14). Functional gastrointestinal disorders represent a group of chronic unexplained bowel syndromes, and IBS is the most well-known (16). IBS is characterized by abdominal pain and changing bowel habits, with a prevalence of 7–10% in the general population (17). In another study, the prevalence of IBS was 11% (7). In this study, IBS was diagnosed in 30% of the patients with HAE, which is higher than that in the general population. In a study that included patients with familial Mediterranean fever (FMF), 18% had IBS, of which 86.3% had IBS before being diagnosed with FMF (18). Similarly, in this study, most patients had IBS before being diagnosed with HAE. Abdominal pain can be seen in both IBS and HAE; therefore, the delay in diagnosing HAE can be attributed to the diagnosis of IBS. In this study, the delay in diagnosing HAE was also longer in patients with IBS than in those without IBS. Visceral hypersensitivity, abnormal gastrointestinal motility, and psychological disturbances are involved in the pathogenesis of IBS. However, recently, low-grade intestinal inflammation, increased intestinal permeability, and immune activation have also been identified as underlying mechanisms causing IBS (16). Bradykinin is the primary mediator responsible for vascular endothelial inflammation in HAE. Bradykinin receptor-1 (BR-1) is absent in the vascular endothelium under normal physiological conditions. BR-1 is expressed in the vascular endothelium in response to inflammatory stimuli, such as interleukin (IL)-1β and TNF-α, via activation of nuclear factor kappa B (NF-κB) (19). IBS hurts the quality of life and work productivity. It is associated with increased psychological distress, and mental comorbidities such as major depression, and generalized anxiety disorder (20, 21). In this study, frequent attacks and persistent gastrointestinal symptoms other than abdominal attacks were more common in patients with HAE and IBS than in those without IBS. Thus, vascular inflammation and psychogenic factors in IBS may affect the quality of life and work productivity. Patients with IBS have a high rate of exposure to unnecessary surgeries due to abdominal symptoms. In one study, two-thirds of the patients with IBS had seen a doctor within the past 12 months, and 40% of them used medication to relieve their symptoms (22). Similarly, in our study, a gastrointestinal tract-related medical/surgical history was seen more commonly in patients with HAE and IBS. Although abdominal pain is one of the most common symptoms of IBS, bloating, a feeling of incomplete emptying, diarrhea, straining, and constipation may also occur (23). In our study, abdominal pain, and distension were the most common symptoms of IBS.

This study had several limitations. First, it was conducted at a single center and was retrospective. Because HAE is a rare disease, the number of patients included in the study was small. Despite these limitations, the study can guide further larger-scale multicenter studies.

Conclusion

Our study determined the characteristics of IBS seen in HAE. IBS is a diagnosis of exclusion and should be considered after all other causes have been excluded. Clinicians should keep HAE in mind in patients with suspected IBS or those who present with recurrent unexplained abdominal pain. An early diagnosis can lead to prompt treatment and relief of symptoms. Our findings highlight the importance of the association between HAE and IBS for future prospective studies.

Conflict of Interest Statement

It should be stated that there is no conflict of interest: The authors have no conflicts of interest to declare.

Ethical Approval

The study was approved by Necmettin Erbakan University Noninterventional Clinical Research Ethical Committee (Decision no: 2023/4368, Date: 02.06.2023). This article does not contain any studies with human or animal subjects.

Consent to Participate and Publish

The authors declared that getting consent from the patients was unnecessary because the study was a retrospective data analysis.

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Availability of Data and Materials

Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

Authors Contributions

MK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

FÇ, ŞA: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

FSA: Investigation; Validation; Writing-original draft.

RE, MEG: Formal analysis; Investigation; Visualization; Writing-original draft.

EY, TÖ: Funding acquisition; Resources; Supervision; Writing-review & editing.

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