ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2025.879
Asthma Allergy Immunol 2025;23:287-291

RESEARCH ARTICLE

Received: 11.06.2025 • Accepted: 03.09.2025
Online Published: 19.11.2025

Low Prevalence but High Diagnostic Yield: Screening for Hereditary Angioedema in Pediatric Patients with Autoinflammatory Features and Refractory Abdominal Pain

Zulfikar AKELMA[1,2], Seda SIRIN[1,2], Semanur OZDEL[3], Esra BAGLAN[3], Serap OZMEN[2]

[1] Department of Pediatric Allergy and Immunology, Ankara Yildirim Beyazit University, Faculty of Medicine, Ankara, Türkiye
[2] Department of Pediatric Immunology and Allergy, Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, Ankara, Türkiye
[3] Department of Pediatric Rheumatology, Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, Ankara, Türkiye

Corresponding Author: Zülfikar Akelma ✉ akelma@gmail.com

ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of skin and mucosal swelling, potentially leading to life-threatening laryngeal edema. Its gastrointestinal manifestations may mimic those of autoinflammatory diseases such as Familial Mediterranean Fever (FMF), complicating the diagnostic process, particularly in patients resistant to colchicine therapy.

Materials and Methods: This prospective observational study included pediatric patients aged 1-21 years attending the Pediatric Rheumatology clinic between July 2021 and July 2022. Eligible participants either had a diagnosis of FMF confirmed by heterozygous or homozygous MEFV mutations and were resistant to colchicine therapy or displayed autoinflammatory features with non-pathogenic mutations while receiving empirical colchicine treatment. Serum C4 and C1 esterase inhibitor (C1-INH) levels and activity were measured in all patients.

Results: A total of 51 patients (mean age 10.1 ± 4.3 years; 31.4% female) were enrolled. The most frequently reported symptom was abdominal pain (74.5%), followed by fever (43.1%), and joint pain (29.4%). All patients exhibited normal C4 and C1-INH levels, except for one case in which decreased C1-INH activity led to the diagnosis of type II HAE.

Conclusion: This study emphasizes the importance of considering HAE in pediatric patients presenting with persistent abdominal symptoms and suspected autoinflammatory disease, particularly in cases unresponsive to colchicine therapy. The identification of type II HAE in this context highlights the potential for diagnostic overlap and underscores the need for increased clinical vigilance. These findings support the inclusion of HAE in the differential diagnosis of abdominal pain in pediatric patients with autoinflammatory features.

Keywords: Familial Mediterranean Fever, complement C1 inhibitor protein, abdominal pain, angioedema, fever

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by a deficiency or dysfunction of C1 esterase inhibitor (C1-INH). While prevalence is estimated at 1 in 50,000 people, data suggest an increasing incidence. Early and accurate diagnosis is crucial, as delayed diagnosis can lead to serious, potentially life-threatening complications (1).

Familial Mediterranean Fever (FMF), the most common autoinflammatory disease in children, is usually characterized by recurrent episodes of fever and serositis and is responsive to colchicine treatment. HAE is a rare

ORCID Zulfikar Akelma / 0000-0003-0140-5053, Seda Sirin / 0000-0002-9300-5999, Semanur Ozdel / 0000-0001-5602-4595, Esra Baglan / 0000-0001-5637-8553, Serap Ozmen / 0000-0002-5671-9394

bradykinin-mediated disease characterized by recurrent, non-pruritic swelling and abdominal pain and is often confused with inflammatory diseases. In contrast to FMF, which is characterized by interleukin-1-mediated systemic inflammation, HAE results from C1-INH deficiency or dysfunction, leading to excessive bradykinin production. This difference is clinically important because HAE does not respond to colchicine treatment (2).

HAE is divided into Type I, characterized by low C1-INH levels and activity, and Type II, characterized by normal C1-INH levels but low activity (2,3). Typical symptoms of HAE include swelling of the skin and mucosal tissues and life-threatening laryngeal or upper respiratory tract obstruction. In addition, recurrent abdominal symptoms similar to those seen in FMF, TRAPS, Mevalonate Kinase Deficiency, and PFAPA syndrome may also occur. These overlapping features should be carefully considered in the differential diagnosis of HAE (3,4).

This is the first study to evaluate the diagnosis of type I and type II HAE in pediatric rheumatology patients with autoinflammatory features and persistent abdominal symptoms. In this regard, it aims to fill a significant gap in HAE diagnosis. Additionally, patients treated empirically with colchicine but without pathogenic MEFV mutations were included to assess whether unrecognized HAE could account for persistent abdominal symptoms in this diagnostically challenging group.

MATERIALS and METHODS

Study Design and Patient Selection

This prospective observational study was conducted at the Pediatric Rheumatology Clinic of Dr. Sami Ulus Gynecology and Pediatrics Research Hospital between July 2021 and July 2022. Eligible patients were aged 1 to 21 years and experienced recurrent abdominal pain. Patients with genetically confirmed FMF unresponsive to colchicine therapy, as well as those without MEFV mutations but receiving empirical colchicine therapy for persistent abdominal symptoms, were included. None of the patients had received medication known to affect complement levels, such as corticosteroids or biologics. Serum C4 and C1-INH levels and activity were recorded in all patients. Laboratory analyses were performed at Synlab Laboratory (Ankara, Türkiye), an accredited facility operated by Polifarma Pharmaceutical Company in Istanbul, Türkiye. Patient screening followed the diagnostic algorithm for suspected HAE as summarized in the international WAO/EAACI guideline for the management of HAE (5).

All patients were screened during symptomatic periods at the pediatric rheumatology clinic, with abdominal attacks being the primary reason for presentation. Since C4 and C1-INH levels are sensitive to sampling time and laboratory processing methods, strict precautions were implemented. Blood samples were delivered to the laboratory within two hours, following standardized procedures to minimize variability. Functional C1-INH activity was assessed using a conventional ELISA method, which has demonstrated comparability to the chromogenic assay (5). In line with international guidelines, C1-INH concentration <50% of the normal mean were considered diagnostic for type I HAE, while normal or elevated concentrations with reduced activity were indicative of type II in HAE. Normal C1-INH functional activity was defined as 70-130% (5).

Statistical Analysis

Data analysis was conducted using SPSS version 22.0. Categorical variables were reported as frequencies and percentages, while numerical variables following a normal distribution were expressed as means ± standard deviations, and those with a non-normal distribution were presented as medians with interquartile ranges. Differences in frequencies were assessed using the Chi-square test or Fisher's exact test, with statistical significance established at a p-value less than 0.05. Due to the absence of prior studies, a sample size calculation could not be performed.

The study was approved by the Ethics Committee of Dr. Sami Ulus Maternity and Children Training and Research Hospital (approval number: E-21/06-189). Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. AI tools (ChatGPT, OpenAI, San Francisco, USA) were used for language editing.

RESULTS

A total of 51 patients were enrolled in the study, with a mean age of 10.11 ± 4.33 years. Of these, 16 (31.4%) were female, and 35 (68.6%) were male. The most common symptom was abdominal pain reported in 38 patients (74.5%), followed by fever in 22 (43.1%), and joint pain in 15 (29.4%). Demographic and clinical features are presented in Table I.

Table I: Demographic and clinical findings of the patients.

	n=51
Age, years (Mean ±SD)	10.1±4.3
Age at symptom onset, years (Mean ±SD)	4.8 ± 4.0
Gender, n (%)	
Girl	16 (31.4)
Boy	35 (68.6)
Abdominal pain, n (%)	38 (74.5)
Fever, n (%)	22 (43.1)
Arthralgia, n (%)	15 (29.4)
Vomiting, n (%)	6 (11.8)
Diarrhea, n (%)	4 (7.8)
Nausea, n (%)	6 (11.8)
Bloating, n (%)	6 (11.8)
Chest pain, n (%)	4 (7.8)
Joint swelling, n (%)	8 (15.7)
Increased joint temperature, n (%)	7 (13.7)
Additional allergic symptom in any attack, n (%)	32 (62.7)
Increased APR during an attack, n (%)	19 (37.3)
Family history of the Autoinflammatory disease, n (%)	14 (27.5)
Attack period; day, median (min-max)	30 (1-180)
Triggers caregivers reported, n (%)	15 (29.4)
Food	6
Infections	2
Exercise	1
Drug	2
Cold	2
Stress	2
Concomitant allergic disease, n (%)	15 (29.4)

APR: Acute phase reactant

Table II: Mutation screening of the Autoinflammatory Disease genes (n=25).

	n (%)
Normal	13 (52.0)
A744S heterozygous	1 (4.0)
E148Q heterozygous	2 (8.0)
M6801 homozygous	1 (4.0)
M694V heterozygous	4 (16.0)
m694v homozygous	1 (4.0)
P369S heterozygous	1 (4.0)
R202Q homozygous	1 (4.0)
TNSFR heterozygous	1 (4.0)
Total	**25 (100.0)**

Serum C4 and C1 esterase inhibitor levels were within normal ranges for all patients. However, one patient exhibited a reduced C1 esterase inhibitor function ratio, leading to a confirmed diagnosis of Type II HAE. Genetic testing was conducted in 25 of the 51 patients, revealing no mutations in 16 cases. Mutation screening results for genes associated with autoinflammatory disorders are shown in Table II.

Case Evaluation: HAE Type II

A 9-year-old girl presented with recurrent abdominal pain and intermittent low-grade fevers, which began at 8 months of age. She also experienced occasional arthralgia during episodes. Her parents were non-consanguineous. Her sister with similar symptoms had responded to colchicine therapy, and her mother was later noted to have recurrent abdominal pain and bloating.

Initially, PFAPA syndrome was suspected; however, the clinical findings did not meet FMF diagnostic criteria. Genetic analysis, including MEFV testing and a comprehensive autoinflammatory panel, revealed no pathogenic variants. Laboratory evaluation demonstrated normal C4 (0.26 g/L; reference 0.1-0.4 g/L) and normal C1-INH concentration (27.4 mg/dL; reference 21-38 mg/dL). Nevertheless, C1-INH activity was decreased in two separate measurements (46% and 39%). Review of prior hospital records confirmed decreased C4 levels during abdominal attacks.

After a diagnostic delay of approximately nine years, Type II HAE was confirmed. Her mother was also found to have low C4 and reduced C1-INH activity (0.04 g/L and 19%, respectively) despite normal C1-INH concentration. SERPING1 genetic testing is planned for both the patient and family members. Following diagnosis, management was initiated according to established HAE guidelines. Colchicine therapy was ineffective in this patient, in contrast to her sister.

This case underscores the prolonged diagnostic delay and emphasizes the importance of accurate laboratory evaluation in differentiating recurrent abdominal pain syndromes.

DISCUSSION

HAE is a rare condition that often presents with abdominal pain, a feature that may overlap with FMF. This results in diagnostic errors and inappropriate treatment,

especially in endemic areas of FMF. Several reports have described patients initially diagnosed with FMF, including those with MEFV mutations, who were subsequently identified as having HAE when symptoms persisted despite colchicine therapy (6).

Abdominal pain is the second most common manifestation of HAE after peripheral swelling, yet it is frequently underrecognized (7). Abdominal pain results from transient intestinal wall edema and typically begin during the first decade of life. Diagnosing abdominal pain in children is particularly challenging due to its broad differential, including gastrointestinal, genitourinary, metabolic, musculoskeletal, and neurological disorders. A review of 19 studies revealed a consistent failure to recognize early warning signs of HAE. Nevertheless, several case reports suggest that gastrointestinal symptoms—such as nausea, bloating, abdominal distension, flatulence, and nonspecific abdominal discomfort—may predict an impending abdominal attack (8,9). The literature further demonstrates that individuals with HAE commonly suffer from recurrent abdominal pain, often contributing to diagnostic delays. The majority of these patients are commonly misdiagnosed with primary gastrointestinal disorders including irritable bowel syndrome, recurrent pancreatitis, appendicitis, or colonic intussusception (10). A 15-year-old girl with a homozygous MEFV mutation who had recurrent abdominal attacks with hand swelling, and showed poor response to colchicine was subsequently diagnosed with coexisting Type I HAE. Her symptoms persisted every two months despite the absence of additional mutations (11). Similarly, a 24-year-old patient misdiagnosed with FMF and who failed to improve with colchicine therapy was diagnosed with Type II HAE after reduced C1-INH activity and a SERPING1 mutation were identified (12). Although *R202Q* mutations are considered benign; we suggest that this patient's clinical features were attributable to HAE, consistent with our findings (13). Another patient with impaired C1-INH function and SERPING1 mutations who failed FMF therapy was subsequently diagnosed with Type II HAE (14). The oldest reported case is a 78-year-old veteran with persistent, unexplained abdominal and gastrointestinal complaints (15).

Unusual manifestations of rare disorders can lead to overlapping symptoms, complicating the diagnosis. HAE may mimic conditions such as FMF or autoimmune conditions such as Behçet's disease and PFAPA syndrome. On average, patients with HAE consult 4.4 physicians over a period of 8.3 years before receiving an accurate diagnosis. In our study, one patient's symptoms began at 8 months of age, but was not diagnosed for 9 years illustrating how limited awareness of HAE and overlapping clinical features contribute to prolonged diagnostic delays (16).

Our case highlights the importance of family history and the critical role of HAE screening. At the same time, the patient's mother also reported recurrent abdominal symptoms and was found to have reduced C4 and C1-INH activity. This underscores the importance of family evaluation, as identifying affected relatives not only enables earlier diagnosis but also prevents unnecessary therapies and prolonged treatment courses (17).

These findings emphasize the importance of considering HAE in pediatric patients presenting with unexplained abdominal pain, particularly if colchicine-resistant FMF or other autoinflammatory diseases are suspected. Unfortunately, abdominal pain episodes are often misdiagnosed as gastrointestinal disorders such as irritable bowel syndrome, appendicitis, or pancreatitis, contributing to diagnostic delays. Although the detection of only one HAE case (1/51) in our study limits the generalizability of our study, clinicians should keep in mind that symptoms such as nausea, bloating, and distension may be warning signs of an HAE attack. Larger studies are needed to confirm the observations in our study.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate HAE among pediatric patients presenting with autoinflammatory features and unexplained abdominal pain. Because its symptoms mimic those of FMF and other autoinflammatory diseases, HAE is often overlooked in clinical practice, and this is further complicated by clinicians' limited awareness. While the identification of only one case of HAE limits its generalizability, our study highlights the importance of recognizing this diagnostic possibility and encourages further research to better define overlapping features.

Conflict of Interest

All authors confirm that they have no conflicts of interest to disclose.

Author Contributions

Concept: **Zulfikar Akelma, Seda Sirin, Semanur Ozdel,** Design: **Zulfikar Akelma, Seda Sirin, Semanur Ozdel, Esra Baglan,** Data collection or processing: **Zulfikar Akelma, Seda Sirin, Sema-**

nur Ozdel, Esra Baglan, Serap Ozmen, Analysis or Interpretation: **Zulfikar Akelma, Seda Sirin, Semanur Ozdel,** Literature search: **Zulfikar Akelma, Seda Sirin, Semanur Ozdel, Esra Baglan,** Writing: **Zulfikar Akelma, Seda Sirin,** Approval: **Zulfikar Akelma, Seda Sirin, Semanur Ozdel, Esra Baglan, Serap Ozmen.**

REFERENCES

1. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med 2008;359(10):1027-36.
2. Schutt C, Siegel DM. Autoinflammatory Diseases/Periodic Fevers. Pediatr Rev 2023;44(9):481-90.
3. Davis AE. Hereditary angioedema: a current state-of-the-art review, III: mechanisms of hereditary angioedema. Ann Allergy Asthma Immunol 2008;100(1 Suppl 2).
4. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract 2021;9(1):132-50.e3.
5. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. Allergy: European Journal of Allergy and Clinical Immunology 2022;77(7):1961-90.
6. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31(5):407-14.
7. Beken B, Akin E, Dogan S, Kasapcopur O. Rare coexistence in pediatric practice: Hereditary angioedema and familial mediterranean fever. Pediatr Allergy Immunol 2022;33(2):e13747.
8. Kemp JG, Craig TJ. Variability of prodromal signs and symptoms associated with hereditary angioedema attacks: a literature review. Allergy Asthma Proc 2009;30(5):493-9.
9. Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. Immunol Allergy Clin North Am 2006;26(4):653-68.
10. Patel N, Suarez LD, Kapur S, Bielory L. Hereditary Angioedema and Gastrointestinal Complications: An Extensive Review of the Literature. Case Reports Immunol 2015;2015:1-8.
11. Bahceci SE, Genel F, Gulez N, Nacaroglu HT. Coexistence of hereditary angioedema in a case of familial Mediterranean fever with partial response to colchicine. Cent Eur J Immunol 2015;40(1):115-6.
12. Sim DW, Park KH, Lee JH, Park JW. A Case of Type 2 Hereditary Angioedema With SERPING1 Mutation. Allergy Asthma Immunol Res 2016;9(1):96.
13. Çapraz M, Düz ME. R202Q prevalence in clinically diagnosed Familial Mediterranean Fever patients: 9 years of data analysis from 1570 patients living Central Black Sea region, Turkey. Ir J Med Sci 2023;192(5):2273-8.
14. Barešić M, Karanović B, Coen Herak D, Kozmar A, Anić B. Misleading symptoms of hereditary angioedema type II mimicking familial mediterranean fever. Acta Reumatol Port 2020;45(2):143-6.
15. Berger J, Carroll MP, Champoux E, Coop CA. Extremely Delayed Diagnosis of Type II Hereditary Angioedema: Case Report and Review of the Literature. Mil Med 2018;183(11-12):E765-7.
16. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? Ann Allergy Asthma Immunol 2010;104(3):211-4.
17. Abass MK, Dabosy A, Walid Khawaja K, Fischer PR. Repeated attacks of hereditary angioedema in pediatric female. Paediatr Int Child Health 2024;44(1):39-41.