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The Clinical and Demographic Characteristics of Our Hereditary Angioedema Patients: A Single-Center Experience

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ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare disease associated with significant morbidity and mortality, particularly due to laryngeal attacks. This study aimed to describe the demographic and clinical characteristics of adults with HAE followed at a single center, with a focus on triggers, diagnostic delay, and treatment approaches.

Materials and Methods: This retrospective cohort study included 15 patients aged ≥18 years who were followed at our center between 2019 and 2024. Clinical and laboratory data were obtained through retrospective review of medical records.

Results: Fifteen HAE patients were included; 73.3% were female (median age: 34 years, range: 21–73). The diagnostic delay was 8 years (range: 0–49), and patient age was positively correlated with diagnostic delay (r=0.706, p=0.003). Thirteen patients had HAE-1 and two HAE-2; attacks most commonly involved the face/extremities (46.7%) and gastrointestinal tract (33.3%). Laryngeal attacks occurred in 60% of patients, with 13.3% requiring intensive care unit (ICU) follow-up but no intubation. Attacks were most frequently reported by patients in association with stress or fatigue (86.7%), followed by trauma. Among female patients, 27.3% reported a temporal association between menstrual cycles and attack occurrence. Prodromal symptoms occurred in 66.7%, most commonly skin tightness and tingling. Icatibant was used on demand (median response: 60 min); short-term prophylaxis during procedures (46.7%) prevented attacks. Three patients receiving long-term prophylaxis (LTP) with danazol reported a reduction in attack frequency. Patients with prior ICU admission were more likely to receive LTP (p = 0.029), likely reflecting greater disease severity and reverse causality rather than a causal effect of LTP on ICU admission.

Conclusion: This study provides descriptive real-world data on adults with HAE in a setting with limited access to first-line prophylactic therapies. Stress-related factors were frequently reported in association with attacks, and diagnostic delay appeared to be shorter among younger patients. Restricted access to first-line LTP remains a relevant clinical challenge.

Keywords: Hereditary angioedema, trigger, stress, larynx edema, short-term prophylaxis

INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder affecting approximately 1 in 50,000 individuals worldwide (1-5). Although it is primarily inherited in an autosomal dominant pattern, 20–25% of cases result from de novo mutations (6-8). The primary mediator in the pathophysiology of HAE is bradykinin, a vasoactive nonapeptide that increases vascular permeability (1,9). Based on current knowledge, HAE is classified into two main types: the more common C1 inhibitor (C1-INH)-HAE, caused by a deficiency (C1-INH-HAE type-1, HAE-1, 85%) or dysfunction (C1-INH-HAE type-2, HAE-2, 15%) of C1-INH, and the less common non-C1-INH-HAE forms, characterized by normal C1-INH levels and function (1,7,10).

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Approximately half of patients with HAE experience recurrent angioedema attacks by the age of ten, with most becoming symptomatic before the age of 20, and symptoms often worsening during adolescence (10-12). HAE attacks can affect any part of the body, most commonly involving the extremities, face, oropharynx, gastrointestinal tract, and genitalia (1,13,14). Oropharyngeal involvement is particularly concerning due to the risk of airway obstruction and asphyxia, which may lead to mortality (15,16). Although some studies suggest a reduction in diagnostic delay in C1-INH-HAE over time, delayed diagnosis remains a major clinical challenge, particularly in patients with oropharyngeal involvement due to its life-threatening potential (13,17,18). Beyond the physical risks, attacks also cause severe pain, psychological distress, and significantly impair quality of life (QoL) (19). Known triggers for attacks include stress, physical trauma, and infections, although attacks may also occur without identifiable precipitating factors (1,20-22). Notably, recent studies have identified sexual intercourse as a potential trigger for genital and abdominal attacks in some patients (23,24).

According to the guidelines of the World Allergy Organization and the European Academy of Allergy and Clinical Immunology (WAO/EAACI), the primary goal of HAE management is comprehensive disease control (1). Effective prevention of attacks and improvement of patients' QoL are necessary for complete disease control. In this context, patient and family education (e.g., knowledge of attack triggers, contraindicated drugs, recognition of prodromal symptoms, on-demand treatment, and situations in which short-term prophylaxis (STP) should be given) is critical for disease control (1).

The aim of this study was to evaluate the demographic characteristics, triggers, and treatment approaches of HAE patients followed and treated at our clinic and to contribute to the existing literature on this rare disease.

MATERIALS and METHODS

Study Design

This retrospective study included patients aged 18 years or older who were diagnosed with HAE according to WAO/EAACI guidelines and treated or followed up at our adult allergy and immunology center between 2019 and 2024. The study was conducted in accordance with the ethical standards of the local ethics committee, and ethical approval was obtained (approval number: TABED 2-24-451).

A retrospective review of electronic health records identified 27 patients diagnosed with HAE who presented to our center during the study period. Of these, 12 patients were excluded from the study due to a lack of regular follow-up at our center. The primary reasons for their visits included prescription renewal requests after depletion of on-demand treatments provided by other centers, as well as consultations related to childbirth or surgical procedures referred by other specialties. Consequently, 15 patients with complete clinical data and consistent follow-up at our center were included in the analysis, while those with incomplete data were excluded (Figure 1). This inclusion strategy was applied to ensure data completeness and reliable longitudinal assessment in a real-world clinical setting. Among the patients screened and followed at our center during the study period, none fulfilled diagnostic criteria for non–C1-INH HEA.

Data Collection

All evaluated parameters are routinely assessed during clinical visits of patients with HAE, and laboratory tests are requested as part of the standard diagnostic workup. Data collected for the study included patient demographics, age at symptom onset and at diagnosis, duration of diagnostic delay, C4 levels, C1-INH mass/function levels, HAE type, presence of prodromal symptoms, attack triggers, monthly attack frequency, most frequent attack sites, HAE treatments, including on-demand therapy and long-term prophylaxis (LTP), and STP status, if applicable. Data were obtained through a retrospective review of patient records. Patients with incomplete clinical data were excluded from the analysis to minimize missing data and ensure consistency across evaluated variables.

Statistical Analysis

Data analysis was performed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation for variables with a normal distribution, and median (range) for non-normally distributed data. Nominal variables were expressed as frequency (n) and percentage (%) and were assessed using Pearson's chi-square test or Fisher's exact test. The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests, along with probability plots and histograms. A p-value of less than 0.05 was considered statistically significant. Given the small sample size, all statistical analyses were considered exploratory.

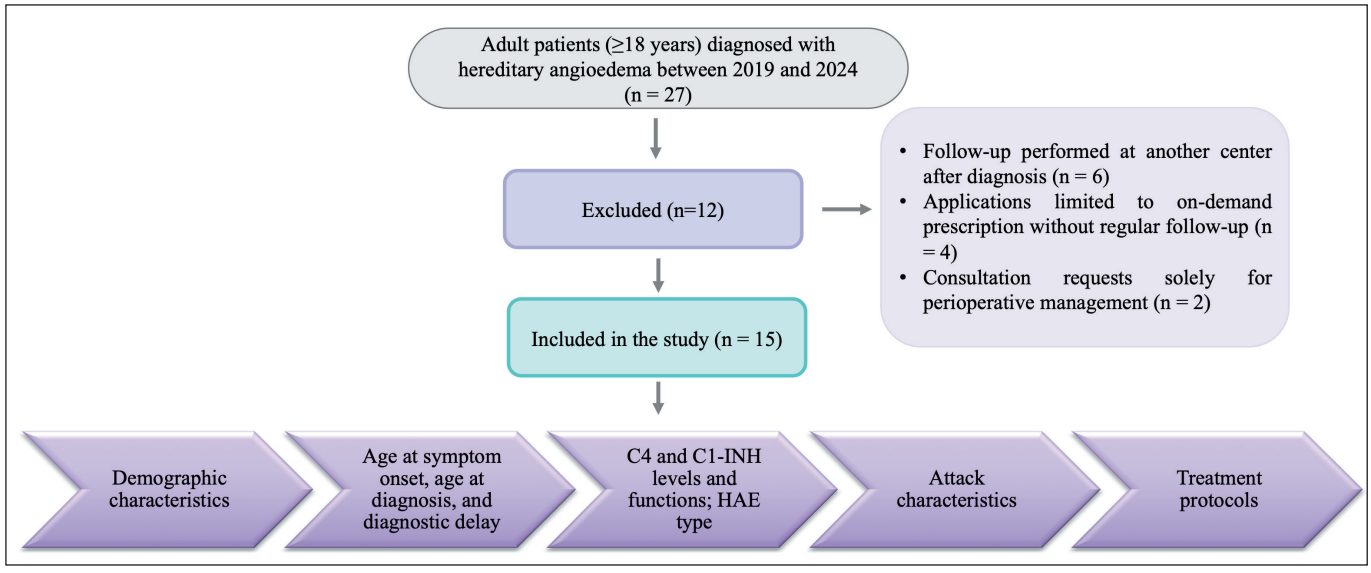

Figure 1: Study flow chart of patients with hereditary angioedema included in the study.
Adult patients (≥18 years) diagnosed with hereditary angioedema between 2019 and 2024 were screened. Patients with regular follow-up at our center and complete clinical data were included. Reasons for exclusion are shown. Data collected are summarized at the bottom of the figure.
C4: *complement 4;* **C1-INH:** *C1 inhibitor;* **HAE:** *hereditary angioedema.*

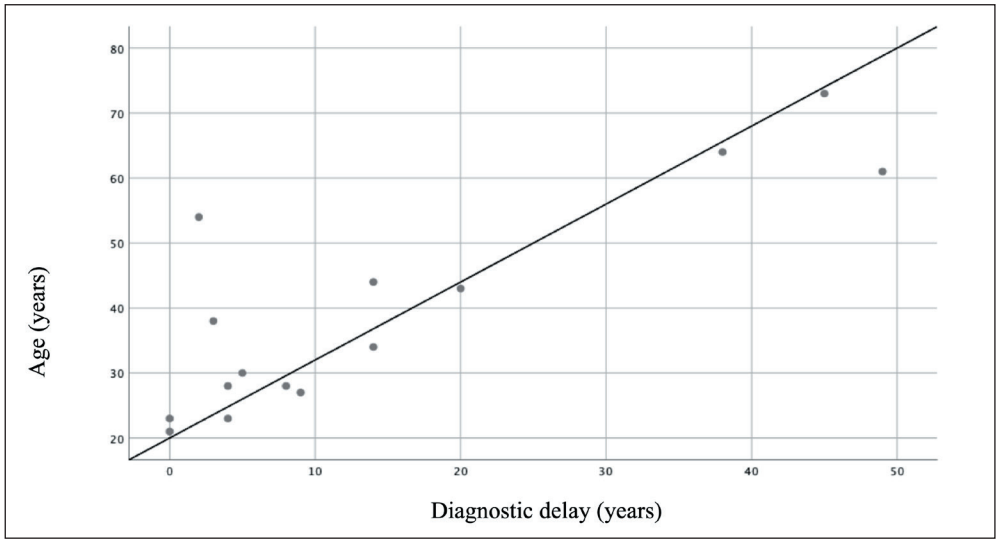

Figure 2: Correlation between patient age (years) and diagnostic delay (years).
Scatter plot showing the relationship between patient age and diagnostic delay. Each dot represents one patient. The solid line represents the linear regression line (r = 0.706, p = 0.003).

RESULTS

Demographic and Laboratory Characteristics

Fifteen patients with HAE were included in the study, 11 (73.3%) of whom were female. The median age of the cohort was 34 years (range: 21–73). Two patients (13.3%) had consanguineous parents, eight (53.3%) had a family history of HAE, and six (40%) reported a family history of HAE-related deaths. Educational status varied among patients; one patient was illiterate and seven (46.7%) were employed. Two patients (13.3%) had comorbidities other than HAE, one of which was histaminergic urticaria.

The median age at symptom onset was 14 years (range: 4-52), and the median age at diagnosis was 29 years (range: 4-59). The median diagnostic delay was 8 years (range: 0-49). There was a strong positive correlation between age and diagnostic delay (r = 0.706; p = 0.003) (Figure 2). Thirteen patients were diagnosed with HAE-1 and two with

HAE-2. Detailed demographic characteristics and laboratory findings at diagnosis, including serum C4 levels and C1-INH concentration and functional activity, are shown in Table I.

Clinical Characteristics and Treatment Responses

At diagnosis, the most common attack sites were the face (46.7%, n = 7), extremities (46.7%, n = 7), and gastrointestinal tract (33.3%, n = 5). Sixty percent of patients (n = 9) reported at least one lifetime laryngeal attack, and two patients (13.3%) required intensive care unit (ICU) monitoring; none required intubation.

Six patients experienced laryngeal attacks (five had one episode, and one had two episodes) before the diagnosis whereas three patients reported laryngeal attacks after the diagnosis (one had four episodes, and two had one episode). All patients identified at least one trigger, most commonly stress or fatigue (n = 13) and trauma (n = 8). Among female patients, three of eleven (27.3%) reported the menstrual cycle as a trigger. Four of seven patients with a history of pregnancy experienced increased attack frequency during pregnancy, with variable patterns across pregnancy and breastfeeding periods.

Prodromal symptoms were reported by 66.7% of the patients (n = 10), most frequently skin tightness (n = 6/10), tingling (n = 6/10), pruritus (n = 5/10), fatigue (n = 4/10), and weakness (n = 4/10); none reported erythema marginatum. The median number of attacks per month was 2 (range: 1–12), and two patients (13.3%) experienced more than six attacks per month. The most commonly affected areas during attacks were the extremities (n = 8, 53.3%), particularly the hands, feet, and knee joints, followed by the face (n = 6, 40%), most frequently involving the eyes and lips, and the gastrointestinal tract (n = 5, 33.3%).

All patients had access to icatibant for on-demand treatment; however, four patients sought emergency department care during attacks despite this availability. Among these patients, the most common attack sites were the face (n = 2), gastrointestinal tract (n = 1), and extremities (n = 1). The response time to icatibant was 60 minutes or less in 10 patients, with a median response time of 60 minutes (range: 10-240 minutes).

STP was administered to 46.7% of the patients, including during delivery (n = 2), tooth extraction (n = 3), nasal septoplasty (n = 1), and both tooth extraction and cesarean section (n = 1). Intravenous plasma-derived C1-INH

Table I: Demographic, laboratory, and clinical characteristics of the study group (n = 15)

Characteristic	Value
Demographic characteristics	
Female sex, n (%)	11 (73.3)
Age, years, median (range)	34 (21–73)
Education status	
Illiterate	1 (6.7)
Primary school	6 (40.0)
High school	3 (20.0)
University	5 (33.4)
Disease characteristics	
HAE type 1, n (%)	13 (86.7)
HAE type 2, n (%)	2 (13.3)
Age of symptom onset, years, median (range)	14 (4–52)
Age at diagnosis, years, median (range)	29 (4–59)
Diagnostic delay, years, median (range)	8 (0–49)
Family history of HAE, n (%)	8 (53.3)
Family history of HAE-related death, n (%)	6 (40.0)
Laboratory findings	
Serum C4, mg/dL, median (range) (reference: 10–40 mg/dL)	5 (0–10)
Serum C1-INH level, mg/dL, median (range) (reference: 21–38 mg/dL)	8.5 (0.1–29.1)
Serum C1-INH functional activity, %, median (range) (reference: 70–132%)	18 (0–71)
Clinical characteristics	
Attack areas at diagnosis, n (%)	
Face	7 (46.7)
Extremity	7 (46.7)
GIS	5 (33.3)
Laryngeal attack history, n (%)	9 (60.0)
Before diagnosis	6 (40.0)
After diagnosis	3 (20.0)
Median number of attacks per month (range)	2 (1-12)
Triggers and prodromal symptoms	
Stress and fatigue, n (%)	13 (86.7)
Trauma, n (%)	8 (53.3)
Prodromal symptoms (n = 10), n (%)	
Skin tightness and tingling	6 (60.0)
Pruritus	5 (50.0)
Fatigue and weakness	4 (40.0)
Treatment characteristics	
Patients undergoing STP, (n%)	7 (46.7)
Birth	2 (28.6)
Dental treatment	3 (42.8)
Dental treatment and birth	1 (14.3)
Nasal septoplasty	1 (14.3)
Patients who underwent LTP, n (%)	3 (20.0)
LTP rejection due to fear of side effects, n (%)	4 (26.6)

HAE: Hereditary angioedema; **C1-INH:** C1 esterase inhibitor; **mg:** milligram; **dl:** deciliter; **STP:** short-term prophylaxis, **LTP:** long-term prophylaxis

(pdC1-INH) concentrate was used for STP, and no post-procedural attacks were observed.

Three patients with a history of frequent attacks and prior ICU admission were initiated on LTP with danazol as second-line therapy and subsequently reported a reduction in monthly attack frequency. However, four patients who were advised to initiate LTP declined danazol due to concerns about potential side effects. The clinical characteristics and treatment responses of the patients are summarized in Table I.

No statistically significant differences were observed with respect to gender, HAE type, joint, gastrointestinal, or facial involvement at diagnosis, prodromal symptoms, laryngeal attack history, or attack frequency (all $p > 0.05$). Similarly, having more than six attacks per month was not significantly associated with gender, HAE type, clinical involvement at diagnosis, prodromal symptoms, laryngeal attacks, or LTP use. Patients with prior ICU admission were more likely to receive LTP (100% vs. 7.7%, $p = 0.029$), a finding that should be interpreted cautiously given the small sample size and the possibility of reverse causality.

DISCUSSION

This study provides valuable insights into the diagnostic delays and treatment strategies in HAE. Our findings suggest shorter diagnostic delays among younger patients, which may reflect increased awareness and improvements in diagnostic practices over time. Importantly, stress was the most frequently reported trigger for attacks, highlighting an important management challenge. Additionally, in this study, reluctance toward LTP was observed in some patients who were recommended LTP, possibly related to concerns about the side effects of second-line LTP agents. These findings emphasize the critical need to enhance access to first-line LTP treatments and suggest that improving HAE management requires a multifaceted approach to bolster treatment efficacy and patient outcomes.

The median age of attack onset in our patients was consistent with data reported in the literature (10-13). However, it is noteworthy that approximately half of the patients did not report a family history of HAE. This proportion appears higher than reported in the literature and may be attributed to the small size of our cohort or the potential presence of undiagnosed relatives among our patients (1,6-8). These findings highlight the necessity of a comprehensive diagnostic approach, as relying solely on family history could lead to missed diagnoses.

Diagnostic delay remains a significant challenge for patients with HAE, as is often the case with rare diseases. The literature indicates that average diagnostic delays range from 1.4 to 8.5 years, with some reports describing longer delays of 13–20 years (12,17,20). Although increased awareness and advances in diagnostic practices may have contributed to shorter diagnostic delays in more recently diagnosed patients, delayed diagnosis continues to pose critical risks, including prolonged morbidity and a markedly elevated mortality risk during laryngeal attacks (12,13,15,17,18,20,25,26). In our study, younger patients were observed to have shorter diagnostic delays, with a median delay of eight years. This observation is in line with reports suggesting a trend toward earlier diagnosis; however, diagnostic delay remains an ongoing problem. In our cohort, 40% of patients had a family history of mortality due to laryngeal edema, and more than half had experienced at least one laryngeal edema attack during their lifetime. Similarly, 65.6% of 107 Brazilian patients reported at least one laryngeal attack, with attacks being more frequent and severe in women (27). In our cohort, although laryngeal edema attacks were also more common among women, this difference did not reach statistical significance.

In some HAE patients, attack triggers and prodromal symptoms can be identified before attacks, while in others, no such triggers or symptoms are detectable. Additionally, the nature of attacks may not always be consistent, even in the same patient (1). In our study, emotional stress, fatigue, and trauma were the most commonly reported attack triggers, consistent with the literature (13). Furthermore, one-third of female patients reported the menstrual cycle as a trigger. Although some studies emphasize that sexual activity can trigger genital and/or abdominal attacks, there were no patients in our patient records who identified it as an attack trigger (23,24). This discrepancy may reflect the retrospective nature of our study or underreporting influenced by cultural factors. Prodromal symptoms were reported by more than half of our patients, similar to previous studies, where symptoms such as fatigue, skin tightness, and tingling were common (13,28). Unlike the literature, which describes erythema marginatum in up to 30% of cases, none of our patients reported this as a prodromal symptom (13). These findings emphasize the variability in prodromal presentations and attack triggers among HAE patients.

Treatment practices in our cohort aligned with current WAO/EAACI recommendations, including comprehensive education on on-demand therapies and STP (1). All patients had access to icatibant for on-demand treatment and received appropriate education regarding its use. In one study, 52.2% of patients responded to icatibant within 30 minutes (13). In comparison, 40% of our patients achieved symptom improvement within 30 minutes, and two-thirds responded within one hour. In previous studies, 11.1% and 12.5% of patients experienced attacks following STP administration (13,29). In our study, pdC1-INH concentrate was administered to seven patients as STP prior to procedures, and no attacks occurred post-procedure. Notably, all patients who required STP after diagnosis successfully received it, underscoring effective management and adherence to prophylactic protocols.

In our country, danazol, an attenuated androgen, is used as a second-line option due to the limited access to first-line agents recommended for LTP such as lanadelumab, berotralstat, and pdC1-INH concentrate. Studies report an average attack reduction rate with danazol, and its oral administration is an added advantage (1). However, this agent is associated with a broad range of side effects, many of which are dose-dependent (30). In our study, three patients with frequent attacks and a history of ICU admission were initiated on danazol as LTP. A reduction in monthly attack frequency was observed in all three patients following LTP initiation. However, four additional patients who were recommended LTP refused danazol due to concerns about its side effect profile. This supports the findings of a recent study in which pharmacophobia towards danazol use was highlighted as a significant problem (13). Beyond treatment-related concerns, the unpredictability of attacks and the potential for genetic transmission impose a significant emotional and psychological burden on patients. A comprehensive review of health-related QoL (HRQoL) in HAE has demonstrated strong associations between frequent attacks and reduced HRQoL across physical, emotional, and social domains, emphasizing the importance of timely diagnosis and effective management. Additionally, barriers such as limited access to treatment agents, adverse effects, and financial constraints persist in some regions, further complicating disease management (19). In light of this information, while our study does not directly assess access to first-line LTP agents, the refusal of danazol among patients due to concerns about side effects may indirectly reflect the ongoing need for safer and more acceptable prophylactic options. These observations suggest that improving access to first-line LTP therapies may be an important component of achieving effective disease control and better patient outcomes.

When interpreting the results of this study, several limitations should be taken into consideration. The retrospective design may have led to underreporting of certain attack triggers or prodromal symptoms, particularly those that are culturally sensitive. In addition, the small sample size and single-center nature of the study limit statistical power and generalizability, increasing the risk of type II error; therefore, the findings should be interpreted with caution and considered as descriptive real-world data rather than inferential. In addition, the small number of female patients limited the ability to perform hormone-related subgroup analyses, and observations regarding menstrual cycle and pregnancy should therefore be interpreted descriptively. The requirement for regular follow-up at our center may have introduced selection bias by excluding patients with sporadic visits or incomplete records. However, this approach was used to ensure data completeness, internal consistency, and reliable longitudinal assessment, in line with the study's aim to descriptively evaluate demographic characteristics, triggers, and treatment approaches of patients with HAE followed in our clinic. Although genetic analysis was not performed, current WAO/EAACI guidelines do not require routine genetic testing for the diagnosis of type I and type II hereditary angioedema. Nevertheless, the inclusion of genetic data could have contributed additional information on genotype–phenotype correlations and familial transmission patterns. The study was descriptive in nature and accordingly did not include a control group. Finally, because of the retrospective and descriptive nature of the study, outcomes were evaluated based on routinely collected clinical data rather than predefined outcome measures. Given the limited sample size, statistical analyses were exploratory, and statistically significant findings should be interpreted as hypothesis-generating rather than confirmatory. Despite these limitations, the study contributes meaningful real-world information on demographic features, diagnostic delay, patient-reported triggers, and treatment practices in hereditary angioedema, supporting its value as a descriptive contribution to the literature on this rare disease.

In conclusion, our study demonstrates that although diagnostic delays in HAE appear to be shorter in younger

patient populations, they remain a persistent challenge, emphasizing the need for comprehensive patient education and effective management strategies, particularly given that stress is a frequently trigger for attacks. Our findings also indicate that limited access to first-line LTP agents may hinder optimal attack control and HRQoL. Early diagnosis, improved access to safer therapies, and strengthened patient education are critical to addressing these challenges. Further research is warranted to validate our findings. Future studies with larger cohorts should focus on evaluating emerging treatment options, incorporating genetic analyses, and developing strategies to overcome barriers to care.

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