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Original article

Demographic and clinical variation in pediatric hereditary angioedema: a single center service evaluation

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SUMMARY

Introduction. Hereditary angioedema (HAE) due to C1 inhibitor deficiency or dysfunction (HAE-C1-INH) is a rare, autosomal dominant condition with recurrent swellings, often beginning in childhood. Pediatric data on disease burden and management are limited.

Materials and methods. We conducted a retrospective review of pediatric HAE cases at Barts Health NHS Trust, London, UK, analyzing clinical features, treatment, and outcomes, comparing symptomatic and asymptomatic patients.

Results. Of 33 children (mean age of 12.9 years), 26 were symptomatic. Median age at first attack was 3.8 years. Facial and abdominal attacks were common; laryngeal attacks rare. 88% had type I HAE. 27% received long-term prophylaxis; 97% held on-demand treatment. Mean AECT score was 11.6.

Discussion. Symptoms and treatment responses varied. Many attacks were untreated despite access to treatment. Prophylaxis was underused and often not first-line.

Conclusion. Pediatric HAE is heterogeneous in presentation. Greater access to modern prophylaxis and better symptom recognition may improve outcomes.

KEYWORDS: Hymenoptera venom allergy, Anaphylaxis, Pediatrics, Children

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INTRODUCTION

Hereditary angioedema (HAE) due to C1 inhibitor deficiency or dysfunction (HAE-C1-INH) is an autosomal dominantly inherited condition with an estimated prevalence of 1 in 50,000, characterized by recurrent swellings affecting the larynx, extremities, face, genitals, and gastrointestinal tract [1]. Key diagnostic biomarkers include low C4 and low or dysfunctional C1-inhibitor (C1-INH). Type I HAE is a quantitative C1-INH deficiency; type II involves reduced C1-INH function [2].

Symptoms of HAE typically begin in childhood, with >50% of patients becoming symptomatic before the age of 10 [3]. Symptoms in children are variable but the majority of attacks, including initial episodes, typically affect the extremities. Abdominal attacks may frequently go unrecognized, as abdominal pain is common and non-specific. Patients may experience diagnostic delay, especially in de novo disease without a family history. Many children are diagnosed through family screening prior to the onset of symptoms. Whilst disease activity can vary between individuals and throughout patients' lives, the impact on

quality of life cannot be understated in affected children. There is a broad variability of disease severity and factors that contribute are not well understood [4].

In the UK, on-demand treatment of acute pediatric HAE attacks often involves C1-INH concentrate or icatibant, and first-line prophylaxis options include C1-INH or lanadelumab, while berotralstat is only licensed for children aged ≥ 12 years and for both disease severity criteria need to be met. For other prophylaxis such as tranexamic acid, there is limited efficacy and safety data for pediatric HAE treatments, and many are used "off-label" [5]. The American College of Allergy, Asthma & Immunology (ACAAI) and the Society for Academic Emergency Medicine (SAEM) have noted the need for more dedicated trials for pediatric-specific treatment [6].

Current international recommendations advise life-long specialist review at least annually, with a focus on optimal symptom control through patient-held rescue medication and, where indicated, long-term prophylaxis [5].

MATERIALS AND METHODS

We audited pediatric HAE patients under the Department of Pediatric Immunology at Barts Health NHS Trust (as of July 30, 2024, audit reference number: 14418). We examined annual review attendance, prophylactic and on-demand treatment approaches, and indicators of disease control. Anonymized data were collected from electronic health records, including age of onset, frequency and nature of attacks, family history, annual reviews, treatments, and clinical outcomes (attack severity, hospitalizations, complications). Descriptive statistics were calculated, with comparative analyses using t-tests, Wilcoxon rank-sum tests, and Chi-square tests in R. This report has been formed from the analysis of results from a registered audit/service evaluation, assessing anonymized data arising from routine care and therefore ethics approval was not required.

RESULTS

Our cohort included 33 children, 18 of whom had a sibling also diagnosed. Basic demographic data is presented in Table I. Overall, 26 (78.8%) had experienced HAE attacks (and thus were defined as symptomatic). The remaining seven were asymptomatic, diagnosed through family screening. The median age was 12.6 years in the symptomatic group (interquartile range (IQR) = 5.9) *vs*. 11.2 in the asymptomatic group (IQR = 4.3, p-value = 0.243). The median age of first attack for symptomatic individuals was 3.8 years (IQR = 7.3). Most children had type I HAE (84.6% of the symptomatic group and 100% of the asymptomatic group). Data on the interval between symptom onset and date of first specialist review for 12 patients with available information are presented in Figure 1. The mean interval was 2.8 years (standard deviation [SD] = 2.7 years).

Clinical characteristics are presented in Table II. Ninety-seven percent of individuals had attended an immunology service review in the prior 12 months. Of the symptomatic patients, 72.7% had at least one attack in that timeframe. The median number of attacks in the last 12 months was 3 (IQR = 9.5). The annual number of treated attacks ranged from 0 to 71. Facial attacks occurred in 38.5% of symptomatic patients, abdominal attacks in 37.5%, and laryngeal attacks in 7.7%. Ten patients had an Angioedema Control Test (AECT) performed with a mean score of 11.6 (SD = 4.2). Of these, 60% scored ≥10, suggesting good control.

All symptomatic patients and over 85% of asymptomatic patients held on-demand C1-INH concentrate. Ten symptomatic patients had additional home treatments; 4 (15.4%) had tranexamic acid, 4 (15.4%) had icatibant, and 2 (7.7%) had both icatibant and C1-INH concentrate to be administered by a trained caregiver.

Seven individuals (26.9%) received long-term prophylaxis: five had tranexamic acid (19.2%), one had subcutaneous C1-INH (3.8%), and one had lanadelumab (3.8%). There were no significant differences in random C4, C1-INH concentration, or C1-INH function between symptomatic and asymptomatic groups.

TABLE I. Basic cohort demographics.

	Symptomatic	Asymptomatic	P-value
N	26	7	
Female, %	11 (42.3%)	2 (28.6%)	0.822
Median age, years (IQR)	12.6 (5.9)	11.2 (4.3)	0.234
Ethnicity:			
White British, %	16 (61.5%)	6 (85.7%)	
White-any other white background, %	2 (7.7%)	0 (0%)	
Asian-Pakistani, %	3 (11.5%)	0 (0%)	
Asian-Bangladeshi, %	5 (19.2%)	0 (0%)	
Other (not stated), %	0 (0%)	1 (14.3%)	
Positive family history, n (%)	20 (76.9%)	7 (100%)	0.372
Median age at presentation, years (IQR)	3.8 (7.3)	--	
Type 1 HAE, n (%)	22 (84.6%)	7 (100%)	
Type 2 HAE, n (%)	4 (15.4%)	0 (0%)	

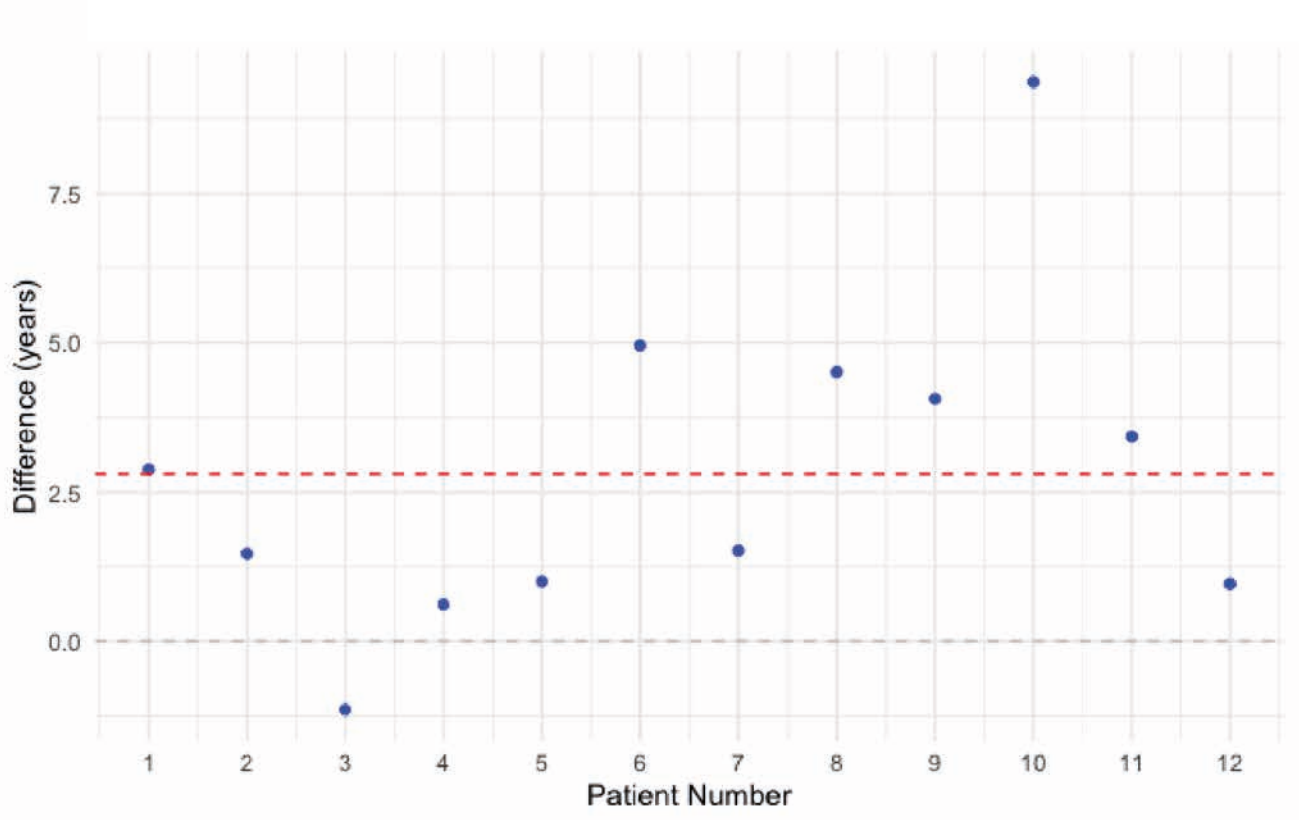

FIGURE 1. Difference between age at presentation and age af first clinic appointment.

DISCUSSION

This single-center audit underscores several key points. First, in terms of clinical features, HAE symptoms can manifest early in life and with variable symptom severity – these findings are consistent with current literature [7]. In addition, regarding abdominal attacks, although common, these may be an underrecognized feature of the disease, as this finding is different to others' reporting cutaneous manifestations to be a more widely reported symptom [7,8]. The proportion of patients with a life-threatening (laryngeal) attack in our cohort is also similar to previous reports [9]. Second, regarding management standards, the vast majority of patients had up-to-date specialist reviews, with nearly all holding emergency on-demand treatment—although many attacks remained untreated, despite guidelines encouraging treatment of all attacks [5]. Third, about one-third of symptomatic patients received long-term prophylaxis, but only a small fraction used first-line prophylactic agents. This finding is similar to previous UK-based reports [9,10]. While most individuals with documented AECT scores had good symptom control, this was not complete and increased access to long term prophylaxis may allow greater control of HAE.

C4 levels and C1-INH function trended lower in symptomatic individuals, though not significantly. C1-INH levels in asymptomatic patients were almost half those in the symptomatic group, reflecting the inclusion of type II HAE cases.

Limitations of this audit include its retrospective, single-center design and reliance on patient-reported data, which may introduce biases. Some records were incomplete, reducing the sample size for certain analyses.

CONCLUSION

Our findings reinforce the clinical variability of pediatric HAE and the need to optimize care. Few studies address pediatric HAE specifically, yet our results highlight the burden of symptoms, the importance of treating attacks, and the desire for broader access to modern prophylaxis in this underserved group.

Ethical considerations

This report was written based on the analysis of results from a registered audit/service evaluation which assessing anonymised

TABLE II. Cohort clinical characteristics.

	Symptomatic	Asymptomatic	Combined	P-value
N	26	7	33	
Number of patients reviewed within last 12 months (%)	25 (96.2)	7 (100)	32 (97)	
Patients with >/= 1 attack in the last 12 months (%)	16 (72.7%)	0 (0%)	-	
Median number of attacks in the last 12 months (IQR)	3 (9.5)	0 (0)	-	
Median number of ED attendances (IQR)	0 (1)	0 (0)	-	
Median number of attacks treated in last 12 months (range)	0 (0-71)	0	-	
Number of patients with facial attacks (%)	10 (38.5%)	0 0%)	-	
Number of patients with abdominal attacks (%)	9 (37.5%)	0 (0%)	-	
Number of patients with laryngeal attacks (%)	2 (7.7%)	0 (0%)	-	
Number of patients with on-demand treatment (%)	26 (100)	6 (85.7)	32 (97)	
Number on a form of home treatment (%)	10 (38.5%)	0 (0%)	-	
Number on long-term prophylaxis, n (%)	7 (26.9%)	0 (0%)	-	
Mean Angioedema Control Test score (range)	11.6 (5-16)	-	-	
C4 level, g/L	0.0576	0.0425	-	0.426
C1 inhibitor concentration, mg/L	126.1	78.3	-	0.447
C1 inhibitor function, %	25.3	27.0	-	0.831

data arising from routine care and therefore ethics approval was not required. As of July 30th 2024, this audit was registered within our Hospital Trusts' audit department with the reference number 14418.

Funding information

This research received no external funding.

Conflict of interest statement

Anthony Dorr has received speaker/consultancy fees, funding to attend conferences and/or participated in advisory boards for Takeda Pharmaceuticals, CSL Behring, BioCryst Pharmaceuticals, and Pharming; has served as a sub-investigator for clinical trials sponsored by KalVista Pharmaceuticals, Ionis Pharmaceuticals and BioCryst Pharmaceuticals; and is a principle investigator for clinical trials sponsored by Pharvaris.

Keith Sacco has received speaker/consultancy fees, funding to attend conferences and participated in advisory boards for Pharming N.V.

Lorena Lorenzo has received grants to attend and participate in educational conferences from Takeda and Biocryst; has served as a resource speaker and as part of the advisory board, and undertaken consulting activity for Biocryst, Pharming and Takeda.

There are no conflict of interests to declare for Rhea Bansal and Mildred Iro.

Authors' contributions

RAB: Conceptualization, methodology and writing original draft. KS: Supervision, writing, review and editing original draft. Anthony Dorr: Supervision, writing, review and editing original draft. LL: Review and editing original draft. MAI: Review and editing original draft.

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