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RESEARCH

Clinical profile and management of pediatric hereditary angioedema in resource-constrained settings: our experience from a single centre in North India

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Abstract

Hereditary angioedema (HAE) is a rare genetic disorder. The pattern of HAE is different in children as compared to adults. There is limited literature from developing countries where all first-line treatments are either unavailable or not easily accessible. Data of children with HAE were retrieved from medical records of patients registered in the Pediatric Immunodeficiency Clinic at our institute. Of the 206 patients with HAE, 61 were diagnosed before the age of 18 years. Male: female ratio was 1.1:1. Median age at onset of symptoms and diagnosis were 6.2 years (range 1–17 years) and 10.7 years (range 1.5–18 years) respectively. Median delay in diagnosis was 4.9 years (range 0–16 years). The commonest presentation was facial swelling (51/61) followed by swelling of extremities (47/61). Laryngeal edema and abdominal symptoms were reported in 28/61 and 31/61 patients respectively. Abdominal attacks were found to be less common in children as compared to adults. Most patients in our cohort received fresh-frozen plasma ($n = 5/61$) as on-demand therapy. Long-term prophylaxis included attenuated androgens ($n = 25/61$) and tranexamic acid ($n = 23/61$). Median duration of follow-up was 2242 patient months. One patient died on follow-up in this cohort. This is the largest single-centre cohort of pediatric HAE from resource-constrained settings. Facial attacks were more common, and there were significant delays in diagnosis when the age of onset of symptoms was younger. Gastrointestinal symptoms were less common in children than adults.

Highlights

- One of the largest single-centre cohorts of pediatric HAE and the only one from resource-constrained settings.
- There were significant delays in diagnosis when the age of onset of symptoms was younger.
- Abdominal attacks were found to be less common in children as compared to adults.

Keywords Hereditary angioedema · C1-esterase inhibitor · Pediatric · Attenuated androgen · Fresh-frozen plasma · Tranexamic acid · Resource-constrained setting · India

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Introduction

Hereditary angioedema (HAE) is an uncommon genetic disorder. Gene defects have most commonly been reported in *SERPING1* gene resulting in decreased or dysfunctional C1 inhibitor (C1-INH) protein levels [1, 2]. HAE with C1-INH deficiency (C1-INH-HAE) is inherited in an autosomal dominant manner; however, about 1/4 of all patients may have de novo mutations [3]. Although clinical symptoms of HAE can manifest at any age; most patients become symptomatic before the age of 18 years [4].

Limited data are available on the clinical profile and outcome of patients with HAE who have been diagnosed in childhood (< 18 years of age) [5–7]. The anatomical and physiological quirks of childhood may predispose them to have a rapid onset of symptoms and severe manifestations including potentially life-threatening upper airway obstruction due to upper airway edema. In addition, the cornucopia of differential diagnoses of abdominal pain in children often causes pediatricians to misidentify abdominal attacks of HAE. Prodromal signs such as erythema marginatum are more common in children; however, they are also more frequently misdiagnosed as urticaria, thereby causing delays in diagnosis [8]. Recent International guidelines have recommended intravenous plasma-derived C1-INH (IV pdC1-INH), recombinant C1-INH, bradykinin B2 receptor antagonist (icatibant) or kallikrein inhibitor (ecallantide) as first-line treatment options for acute treatment of HAE attack, while IV pdC1-INH, subcutaneous pdC1-INH, oral kallikrein inhibitor (berotralstat) or monoclonal antibody against kallikrein (lanadelumab) have been recommended for prophylaxis [1]. However, in resource-constrained settings, such as in India, where these first-line medications are either not available or not easily accessible, one has to resort to second- or third-line drugs with limited efficacy including tranexamic acid (TA), attenuated androgens (AAs) or fresh-frozen plasma (FFP) [1, 8–10]. Herein, we report the clinical profile and outcome of a cohort of patients with HAE from North India who were diagnosed prior to the age of 18 years.

Patients and methods

This retrospective study was conducted in the Pediatric Immunodeficiency Clinic at our institute after clearance from the Department Review Board (APC DRB-05–24, dated 20 February 2024). Data of patients with HAE diagnosed and enrolled in the clinic from January 1996 to May 2023 were retrieved and entered in a predesigned Excel sheet. Pediatric patients with C1-INH-HAE, who were diagnosed before the age of 18 years, were included in the study. Clinical features (age at onset of symptoms, age at diagnosis, site of angioedema episodes, prodromes, and triggers), management (TA, AAs, FFP), and outcomes of these patients were analyzed in detail [including clinical severity score as described by Bygum et al.: age at onset 0–5 years (3 points), age at onset 6–10 years (2 points), age at onset 11–20 years (1 point), age at onset > 20 years (0 points), skin edema (1 point), painful abdominal edema (2 points), laryngeal edema (2 points), other clinical manifestations (1 point), long-term prophylaxis ever (1 point)] [11]. Patients or their guardians/caregivers reported the angioedema episodes based on the recall method. Patients were diagnosed to have C1-INH-HAE if they had characteristic clinical manifestations of the disease with or without a suggestive family history, with low C4 and either a low quantitative C1-INH (type I HAE) [measured using in-house nephelometry] or normal/high C1-INH with low functional activity [measured using enzyme immunoassay] of C1-INH (type II HAE) and/or having a variant in *SERPING1* gene. C1-INH functional analysis, however, could not be performed in majority of patients in the present study as this test is not easily available at our centre. C4 and C1-INH levels were tested once at the time of diagnosis.

Patients with suggestive clinical features but normal C4 and C1-INH and the absence of any known variant in genes known to cause HAE were excluded from the study. Genetic studies were carried out using *SERPING1* gene Sanger sequencing or targeted next-generation sequencing (a panel of 12 genes: *ACE*; *NOS3*; *KLKB1*; *SERPING1*; *PLG*; *BDKRB2*; *KNG1*; *CPN1*; *KLK1*; *ANGPT1*; *CPM*; *F12*). Multiplex ligation-dependent probe amplification (MLPA) was done to evaluate large deletions/duplications in a few cases. We also compared the clinical features of pediatric cohort with that of adult (i.e., > 18 years of age at diagnosis).

Until recently, none of the first-line medications were available in India. Most patients were managed using AAs [stanozolol (1–4 mg/day), danazol (100–600 mg/day)], and/or TA (30–50 mg/kg/day). International guidelines do not recommend AAs as first-line treatment options due to their adverse androgenic/anabolic effects. However, when first-line treatment options are either not available or inaccessible to patients as is the situation in most developing nations including India, most guidelines advocate AAs as second-line therapy with careful monitoring of anticipated side-effects and using the minimal effective dose. In the present study regular clinical examination, 6-monthly blood (lipid profile, liver function tests) and urine tests, and yearly hepatic ultrasonography were done in all patients. On-demand treatment for peripheral and abdominal attacks was initiated at the discretion of the treating physician. However, acute life-threatening laryngeal attacks were managed using

FFP (10–20 mL/kg) or plasma-derived C1-INH (10–20 U/kg) [12]. Long-term prophylaxis (LTP) was initiated at the discretion of the treating physician or in patients who had had at least 1 episode of angioedema per month. All patients were followed up at our centre at 3 to 6-monthly intervals depending on the severity of symptoms. The data were entered into Microsoft Excel worksheets and were analyzed using Statistical Package for Social Sciences (SPSS) version 28. An alpha level of 5% or any *p*-value less than 0.05 was considered significant.

Results

Demographic details

Of the 206 patients diagnosed with HAE in our centre, we included 61 patients (32 boys and 29 girls) with HAE-C1-INH who were diagnosed before the age of 18 years. The median age at onset of symptoms was 6.2 years (range 1–17 years) and the median age at diagnosis was 10.7 years (range 1.5–18 years) with a median delay in diagnosis of 4.9 years (range 0–16 years). Family history was present in 43/61 (70.5%) patients.

Type I HAE was seen in 58 patients, and 3 had type II HAE. C4 levels were reduced in 51 patients (range: < 0.027 to 0.30 mg/L [Normal: 0.14–0.40 mg/L]) and normal in 10 patients at the time of diagnosis. C1-INH levels were low in all patients with type 1 HAE (range: 38 to 164 mg/L [Normal: 195–345 mg/L]). Genetic analysis was performed in 57/61 (93.4%) patients and a pathogenic variant in *SERPING1* gene was identified in 47/57 (82.5%) patients. No pathogenic variant was observed in 10 patients. The commonest mutation was missense (57%) followed by frameshift (23%) and non-sense (20%). The commonest exon involved was exon 7 followed by exon 8, 5, and 3. Patients with HAE type II were diagnosed based on low C4, normal/high C1-INH levels, and a pathogenic variant in *SERPING1* gene.

Clinical manifestations of pediatric HAE

Three children were asymptomatic at diagnosis and during the observation period. They were diagnosed by family screening at the ages of 3, 5, and 6 years respectively. Swelling over the face (eyelids and/or lips) was the commonest presentation (during the observation period) [83.6% (51/61)] followed by extremities and genitalia [77.0% (47/61)] (Table 1). At least one episode of upper airway edema was seen in 45.9% (28/61) cases. Abdominal symptoms were noted in 31/61 (50.8%) of patients. Triggers were noted in 55.7% (34/61) patients with trauma being the commonest trigger ($n = 26$), followed by stress ($n = 8$). Erythema marginatum as a prodromal symptom was observed in 5/61 (8%) patients.

Table 1 Clinical features of pediatric HAE patients

Clinical features	Number of patients ($n = 61$)
Asymptomatic	3 (4.9%)
Swelling over face (lips and/or eyelids)	51 (83.6%)
Swelling of extremities	47 (77.0%)
Swelling of genitalia	13 (21.3%)
Laryngeal edema	28 (45.9%)
Abdominal pain	31 (50.8%)
Tongue swelling	11 (18.0%)
Family history	43 (70.5%)
Prodromes	22 (36.1%)
Triggers	34 (55.7%)
Type I	58 (95.1%)

Table 2 Comparison between pediatric and adult HAE patients in our cohort

Characteristics	Pediatric HAE ($n = 61$)	Adult HAE ($n = 145$)	*p* value
Male:female	32:29	80:65	0.5
Median age at onset (years)	6.2	17.3	**< 0.05**
Median Delays in diagnosis (years)	4.9	21.3	**< 0.05**
Facial swelling	51	113	0.36
Extremity swelling	47	107	0.35
Swelling of genitalia	13	35	0.32
Laryngeal edema	28	82	0.08
Abdominal symptoms	31	94	**< 0.05**
Tongue swelling	11	36	0.14
Prodromes	22	48	0.33
Triggers	34	85	0.42
Clinical severity score (Median)	5	7	0.45

Comparison of pediatric and adult HAE

We compared this cohort and patients with HAE who were diagnosed after the age of 18 years (145 patients) (Table 2). It was observed that older age of onset of symptoms (median 17.3 vs 6.2 years), delays in diagnosis (median 21.3 vs 4.9 years), and abdominal symptoms (94/145 [64.8%] vs 31/61 [50.8%]) were significantly more in adults as compared to pediatric HAE (Table 2). On the other hand, when we analysed the pediatric cohort, it was observed that the delay in diagnosis was higher when age at first symptom was earlier (Pearson correlation coefficient, $r = -0.39$)

suggesting that when symptom onset is earlier there is a greater likelihood that a diagnosis of HAE would be missed as it is often not considered as a differential diagnosis in very young children. We also performed clinical severity score (as described by Bygum et al.) on pediatric and adult patients with HAE in the present cohort. There was no statistically significant difference between clinical severity score in children and adults with HAE (Table 2).

Management of pediatric HAE

Before the diagnosis of HAE was confirmed, nearly all patients received antihistamines, steroids and/or adrenaline. None of the patients in the present series were inadvertently subjected to surgical intervention for abdominal episodes.

Owing to a lack of first-line medications, FFP (10–20 mL/kg) was used for treatment of life-threatening episodes in only 5 patients. Administration of FFP stopped the progression of angioedema episodes in all patients in whom it was administered [12]. The remaining 23 patients who reported a history of laryngeal attacks were not diagnosed to have HAE at the time of their episode and their upper airway edema resolved spontaneously. These episodes were reported by patients as symptoms that were consistent with upper airway edema (i.e., associated with hoarseness of voice and/or difficulty in breathing) and were not observed in hospital. TA (30–50 mg/kg/day) and/or stanozolol (0.5 mg alternate day to 4 mg/day)/danazol (100 mg alternate day to 600 mg/day), adjusted according to symptom control, were used for LTP [AAs ($n=25$, 41%); TA ($n=23$, 38%) and a combination of the 2 drugs ($n=19$, 31%)]. The usual starting dose was stanozolol 1 mg per day and danazol 100 mg per day. The median duration of LTP was 39.9 months (range: 6–264 months). Fifteen patients needed a switch in therapy from AAs to TA or vice versa. This change was necessitated due to unacceptable side effects of androgens or poor response to TA. Androgen therapy was observed to be much more effective than LTP when compared with TA as none of the patients required to be shifted to TA because of no improvement with AA [13]. Side effects of AAs noted were menstrual irregularities ($n=7$), weight gain ($n=9$), acne ($n=5$), hoarseness of voice ($n=4$), hirsutism ($n=4$), acanthosis nigricans ($n=2$), aggressive behavior ($n=2$) and precocious puberty ($n=1$). One patient also developed hypertension. Most side effects were reversible except for precocious puberty in a girl. None of the patients treated with AAs showed overt hepatic or hematological abnormalities. None of the patients on long-term AAs had significant growth arrest.

In the later part of 2022, pdC1-INH was marketed in India for the first time and 2 patients in the present cohort received pdC1-INH for acute management of laryngeal edema. A 14-year-old boy, who had had previous history of life-threatening laryngeal attack with negative pressure pulmonary edema and was treated with FFP at that time had now presented with another episode of laryngeal edema [12]. He was given 1000 IU of IV pdC1-INH, following which his symptoms subsided within 2 h. Another 10-year-old girl presented with an acute abdominal attack, and she was given 500 IU of IV pdC1-INH following which her symptoms subsided within 1.5 h.

Outcome

The total median duration of follow-up of our pediatric cohort, is 2242 patient-months. One patient who was diagnosed at the age of 10 years died at the age of 17 years (before the availability of pd C1-INH). She developed laryngeal edema and died on the way to hospital. In addition, 6 patients in this cohort reported the death of at least one family member due to laryngeal edema [14].

Discussion

"Children are not miniature adults" — most diseases in medicine follow this cardinal rule, and pediatric HAE is no exception. Published literature on pediatric HAE is very limited. There are no previous studies from resource-limited countries where all first-line medications are either unavailable or not easily accessible (Supplementary Fig. 1). In this study, we report the clinical profile of 61 patients with HAE who were diagnosed before the age of 18 years. It was observed that this cohort had significantly fewer gastrointestinal symptoms as compared to patients with HAE who were diagnosed after the age of 18 years.

Most studies have observed that symptoms of HAE usually manifest in the 2nd or 3rd decade of life [5, 7, 15–18]. However, the earliest reported case of HAE was that of a 1-month-old boy from Germany. A recent publication, in fact, also reported a case of HAE in fetal life [19]. In the present study, the age of onset of symptoms was 6.2 years which was slightly higher than the observations from Hungary and Denmark [5, 17]. However, it was similar to studies from USA (5.7 to 7 years) (Table 3). We observed a negative correlation between the age of onset of the first symptom and delay in diagnosis in pediatric HAE patients (Fig. 1). A similar finding was reported by Christiansen et al., wherein the authors observed that HAE in the very young was likely never considered as a differential diagnosis [16].

Previous publications have reported that the initial as well as most frequent attack in children usually involved the abdomen followed by extremities (Table 3) (Fig. 2). This was in contrast to our study where we noted more facial and extremity attacks. Abdominal attacks were significantly more common in adults in our cohort (Table 2). The reason

Table 3 Published literature on worldwide data on pediatric HAE

Author, country, year (Ref)	Total number of pediatric patients	Single/multicentric	Median age of onset (year) [range]	Median delay in diagnosis (year) [range]	Median age at diagnosis (year) [range]	Male:female	Ethnicity	Type of HAE	Presence of trigger (%)	Presence of prodrome (%)	Family history (%)	Treatment	Mortality	Remarks
Farkas, Hungary, 2010 (5)	49	Single	3 [1–7]$^{+}$	2.36^{+}	6 [4–11]	23:26	Eastern Europe	Type I/II^{++}	NA	20 (42)	41 (84)	Acute attacks: NA Short-term prophylaxis: C1INH [$n=8$] Long-term prophylaxis: TA, EACA, danazol [$n=$NA]	None	26/49 children were asymptomatic at diagnosis
Nanda et al., USA, 2015 (7)	21	Single	5.7* [5–9]	6**	5* [4–8]	5:2	Caucasian	***	15 (71.4)	NA	18 (85.7)	Acute attacks: C1INH [$n=9$], AA [1] Short-term prophylaxis: C1INH [$n=10$] Long-term prophylaxis: C1INH [$n=1$], AA [$n=2$]	None	Abdominal attacks > peripheral attacks Delay in diagnosis was more in children without a family history of HAE
Bennett et al., USA, 2015 (15)	25	Single	7	NA	9.5^{+++}	12:13	NA	Type I=25	NA	NA	21 (84)	C1INH: 15 Bradykinin receptor blocker: 7	None	Extremities ($n=10$) > abdominal attacks ($n=9$)

Table 3 (continued)

Author, country, year (Ref)	Total number of pediatric patients	Single/multi-centric	Median age of onset (year) [range]	Median delay in diagnosis (year) [range]	Median age at diagnosis (year) [range]	Male:female	Ethnicity	Type of HAE	Presence of trigger (%)	Presence of prodrome (%)	Family history (%)	Treatment	Mortality	Remarks
Christiansen et al., USA, 2015 (16)	581#	Multi-centric	11 [6–15]	8 [1–16]	19 [12–28]	161:420	NA	Type I=228 Type II=58 Unknown = 295	NA	NA	NA	AA: 476	None	Delay in diagnosis was negatively correlated with age of first swelling
Aabom et al., Denmark, 2017 (17)	22	Single	4 [1–11]	NA	NA	NA	Danish	Type I=19 Type II=3	NA	NA	22 (100)	Acute attacks: C1INH [$n=12$], TA [$n=9$], Icatibant [$n=1$] Short-term prophylaxis: C1INH [$n=5$], TA [$n=4$] Long-term prophylaxis: C1INH [$n=1$], TA [$n=4$]	None	8/22 children were asymptomatic at diagnosis The first attack was more common in extremities ($n=11$), while all 14 symptomatic patients had abdominal attacks subsequently
Aygören-Pürsün et al., USA and Europe, 2017 (18)	6	Multi-centric	NA	NA	10.5 [7–11]	6 females	Caucasian, Mixed	Type I=6	NA	NA	NA	C1INH: 6	None	Abdominal attacks ($n=6$) > peripheral attacks ($n=5$) C1INH is relatively safe and effective in pediatric HAE

Table 3 (continued)

Author, country, year (Ref)	Total number of pediatric patients	Single/ multi-centric	Median age of onset (year) [range]	Median delay in diagnosis (year) [range]	Median age at diagnosis (year) [range]	Male:female	Ethnicity	Type of HAE	Presence of trigger (%)	Presence of prodrome (%)	Family history (%)	Treatment	Mortality	Remarks
Present study, India, 2024	61	Single	6.2 [1–17]	4.9 [0–16]	10.7 [1.5–18]	32:29	Indian	Type I=58 Type II=3	34 (55.7)	22 (36.1)	43 (70.5)	AA-25 TA-23 C1INH-2	2 (1 laryngeal edema; 1 RTA)	Facial attacks ($n=51$) > extremities ($n=47$) > abdominal attacks ($n=31$)

HAE, Hereditary angioedema; *NA*, Not available; *C1INH*, C1-inhibitor; *AA*, Attenuated androgens; *TA*, Tranexamic acid; *EACA*, epsilon-aminocaproic acid; *RTA*, Road traffic accident

* Asymptomatic Children were censored from survival analysis ** Children without family history ($n=3$) had a delay in diagnosis of 6 years ***Both type I and type II HAE patients were included, however, exact number is not available

+ Diagnosis was established after clinical manifestations ($n=10$) + + Exact number not available

+ + + Median age at diagnosis with a positive family history of HAE

#Patients < 21 years of age were included

for this observation is not known. However, one plausible explanation could be that abdominal episodes of HAE may be difficult to recognize in children [1, 8, 20].

Erythema marginatum is an important prodromal symptom in patients with HAE and has been reported in approximately 60% patients in different pediatric series [7, 8, 21]. However, we observed erythema marginatum in 8% of the patients only. This could be because of a darker skin type of Indian children.

Laryngeal attacks in HAE can be life-threatening and may present as the initial symptom in early childhood. In one of the largest cohorts of HAE ($n=123$; including both adults and children), Bork et al. reported that 3.3% of the patients had their first laryngeal attack before the age of 10 years [22, 23]. In the same cohort, the authors reported a 9-year-old boy who had a severe laryngeal attack at the onset of disease and succumbed due to asphyxia [22]. In the present cohort, 46% of the patients had at least one episode of laryngeal edema. With the evolution of first-line treatment options for HAE in most developed countries, mortality due to laryngeal edema has drastically reduced. However, in India and other developing countries, mortality and morbidity due to laryngeal attack continue to be a problem [14]. In the present study, FFP was used as on-demand treatment for laryngeal episodes (only 2 children received pd C1-INH to date). One patient died because of laryngeal edema [14].

Because of the lack of all first-line treatment options for LTP for HAE in India, all patients were managed using AAs and/or TA. None of these therapies have been recommended as first-line treatment options; and in particular, AAs are considered to be contraindicated in children in higher-income countries. However, because of lack of availability, clinicians in most developing countries are still using TA and AAs, even in children [9, 10].

For LTP, several studies have reported use of AAs. A large survey-based study conducted in 2008 from USA reported 81.9% of the patients ($n=476/581$) to have received AAs as LTP. The authors also observed that use of AAs indirectly reflected disease severity [16]. However, most studies published after 2010 from the West have reported gradual decrease in use of AAs in children because of concerns of growth retardation and side effects related to puberty. In the reported literature, AAs were used more often than TA for LTP before the advent of pdC1-INH and other first-line treatment options in developed countries in adults [1, 8]. In the present study, 40.9% (25/61) and 37.7% (23/61) of the children were given AAs and TA respectively. Although adverse effects related to virilisation were commonly seen, AAs were found to be more efficacious than TA. A proportion of patients had to be transitioned from AAs to TA because of side effects and from TA to AAs because of lack of efficacy whereas 31.1% of the patients received a combination of the 2 drugs [9, 13].

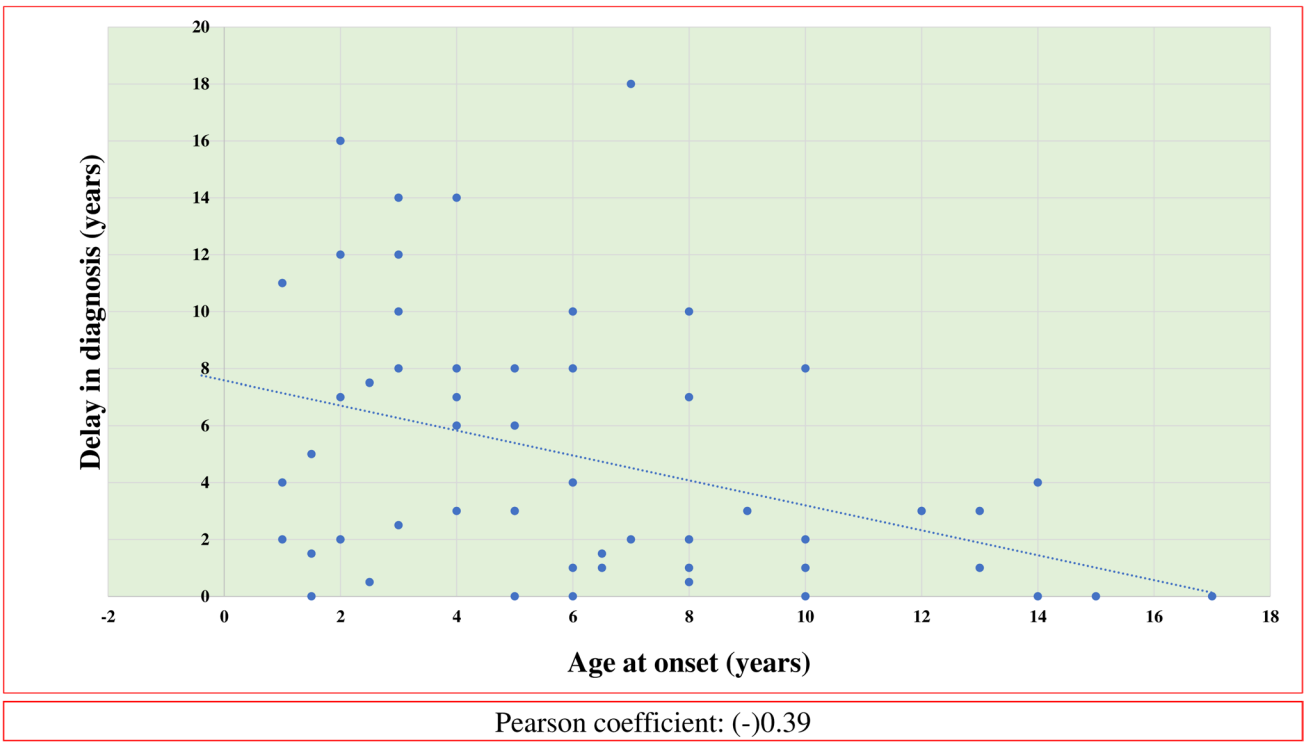

Fig. 1 Scatter plot of pediatric HAE patients in our cohort showing a negative correlation between age at onset and delay in diagnosis

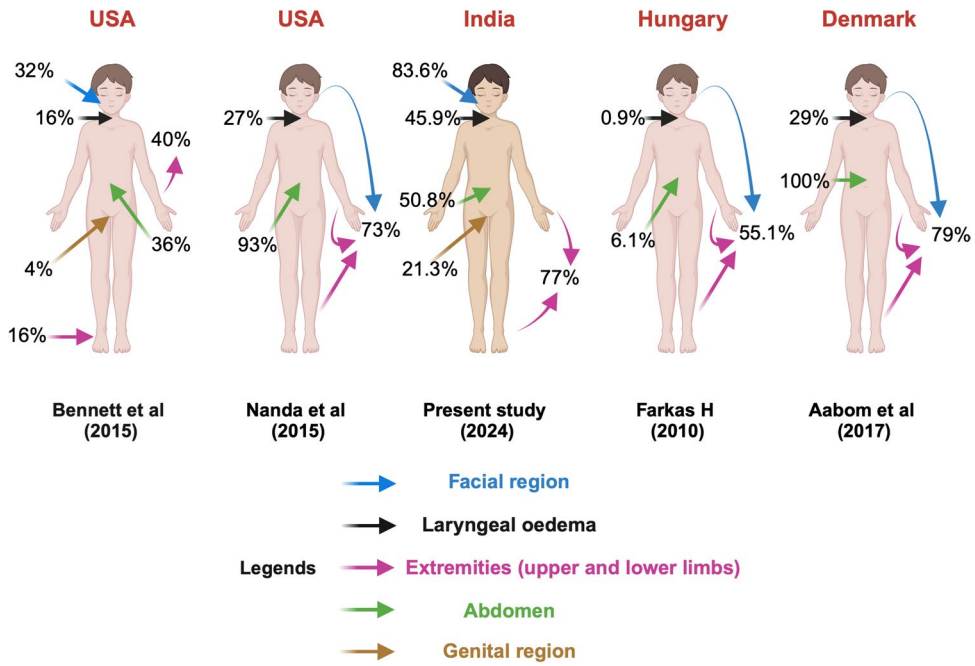

Fig. 2 Frequency of sites involved in pediatric HAE worldwide. Created with BioRender.com

Strength of the study is that this is one of the largest cohorts of pediatric HAE in the world with long-term follow-up. Genetic analysis was performed in 93.4% of the patients in our cohort. The cohort highlighted the difficulties with the management of pediatric HAE in resource-constrained settings.

Limitations include the cross-sectional nature of the study; inability to perform C1-INH function in most patients;

lack of data regarding age-wise distribution of attacks of HAE and effect of puberty on the frequency and severity of episodes. Also, we could not assess if the dose of AAs had a significant association with the efficacy as well as with the adverse effect profile.

The current study highlights the necessity to introduce affordable and accessible first-line medications in India and other low- and middle-income countries.

Conclusion

This is one of the largest single-centre cohorts of pediatric HAE and the only cohort from resource-constrained settings. Facial attacks were more common, and there were significant delays in diagnosis when the age of onset of symptoms was younger. Abdominal attacks were found to be less common in children as compared to adults. With the introduction of pdC1-INH in India, the mortality and morbidity of HAE in children is likely to improve in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12026-024-09547-9.

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Author contributions AKJ: Conceptualization, writing of the initial draft, critical revision of the manuscript and final approval, patient management

PB, SB: writing of the initial draft, revision of the manuscript and patient management.

RT, AS: Writing and editing of the manuscript.

SC, RT, GK, SM: Laboratory investigations, writing and editing of the manuscript.

SD, KV, AB, RS, RG, DS, VP, RP: revision of the manuscript and patient management.

MD, SS, AR, HF, HL, SD, SMK: Laboratory investigations, writing and editing of the manuscript.

SS: Conceptualization, critical revision of the manuscript, patient management.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Department Review Board, Department of Pediatrics of the institute. (APC DRB 05–24; dated 20–2-24).

Consent to participate Informed consent was obtained from all individual participants/family members.

Consent for publication Informed consent was obtained from all individual participants/ family members.

Conflict of interest The authors declare no competing interests.

References

1. 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. 2022;77(7):1961–90.
2. Li PH, Pawankar R, Thong BYH, Fok JS, Chantaphakul H, Hide M, et al. Epidemiology, management, and treatment access of hereditary angioedema in the Asia Pacific Region: outcomes from an international survey. J Allergy Clin Immunol Pract. 2023;11(4):1253–60.
3. Banday AZ, Kaur A, Jindal AK, Rawat A, Singh S. An update on the genetics and pathogenesis of hereditary angioedema. Genes Dis. 2020;7(1):75–83.
4. Rosi-Schumacher M, Shah SJ, Craig T, Goyal N. Clinical manifestations of hereditary angioedema and a systematic review of treatment options. Laryngoscope InvestigOtolaryngol. 2021;6(3):394–403.
5. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol. 2010;6(1):18.
6. Sabharwal G, Craig T. Pediatric hereditary angioedema: an update. F1000Res. 2017;6:F1000 Faculty Rev-1205.
7. Nanda MK, Elenburg S, Bernstein JA, Assa'ad AH. Clinical features of pediatric hereditary angioedema. J Allergy Clin Immunol Pract. 2015;3(3):392–5.
8. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300–13.
9. Jindal AK, Sil A, Aggarwal R, Vinay K, Bishnoi A, Suri D, et al. Management of hereditary angioedema in resource-constrained settings: a consensus statement from Indian subcontinent. Asia Pac Allergy. 2023;13(2):60–5.
10. Jindal AK, Reshef A, Longhurst H. Mitigating disparity in healthcare resources between countries for management of hereditary angioedema. Clin Rev Allergy Immunol. 2021;61(1):84–97.
11. Bygum A, Fagerberg CR, Ponard D, Monnier N, Lunardi J, Drouet C. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency. Allergy. 2011;66(1):76–84.
12. Barman P, Basu S, Thakur I, Chawla S, Kaur A, Jafra A, et al. Negative pressure flash pulmonary edema in a child with hereditary angioedema. Pediatr Allergy Immunol. 2022;33(7):e13825.
13. Jindal AK, Rawat A, Kaur A, Sharma D, Suri D, Gupta A, et al. Novel SERPING1 gene mutations and clinical experience of type 1 hereditary angioedema from North India. Pediatr Allergy Immunol. 2021;32(3):599–611.
14. Kumar Jindal A, Basu S, Tyagi R, Barman P, Sil A, Chawla S, et al. Delay in diagnosis is the most important proximate reason for mortality in hereditary angio-oedema: our experience at Chandigarh, India. Clin Exp Dermatol. 2024;49(4):368–74.
15. Bennett G, Craig T. Hereditary angioedema with a focus on the child. Allergy Asthma Proc. 2015;36(1):70–3.
16. Christiansen SC, Davis DK, Castaldo AJ, Zuraw BL. Pediatric hereditary angioedema: onset, diagnostic delay, and disease severity. Clin Pediatr (Phila). 2016;55(10):935–42.
17. Aabom A, Andersen KE, Fagerberg C, Fisker N, Jakobsen MA, Bygum A. Clinical characteristics and real-life diagnostic approaches in all Danish children with hereditary angioedema. Orphanet J Rare Dis. 2017;12:55.
18. Aygören-Pürsün E, Soteres D, Moldovan D, Christensen J, Van Leerberghe A, Hao J, et al. Preventing hereditary angioedema

attacks in children using Cinryze®: interim efficacy and safety phase 3 findings. Int Arch Allergy Immunol. 2017;173(2):114–9.
19. Grivcheva-Panovska V, Giannetti B. Hereditary angioedema attack in utero and treatment of the mother and fetus. Mayo Clin Proc Innov Qual Outcomes. 2020;4(5):595–600.
20. MacGinnitie AJ. Pediatric hereditary angioedema. Pediatr Allergy Immunol. 2014;25(5):420–7.
21. Ahn YM. Hereditary angioedema in childhood. Clin Exp Pediatr. 2020;63(1):18–9.
22. Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med. 2003;163(10):1229–35.
23. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130(3):692–7.