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ORIGINAL ARTICLE

Novel *SERPING1* gene mutations and clinical experience of type 1 hereditary angioedema from North India

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Editor: Marina Atanaskovic-Markovic

Abstract

Background: There is paucity of literature on long-term follow-up of patients with hereditary angioedema (HAE) from developing countries.

Objective: This study was carried out to analyze the clinical manifestations, laboratory features, and genetic profile of 32 patients (21 male and 11 female) from 23 families diagnosed with HAE between January 1996 and December 2019.

Methods: Data were retrieved from medical records of Paediatric Immunodeficiency Clinic, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Results: Median age at onset of symptoms was 6.25 years (range 1-25 years), and median age at diagnosis was 12 years (range 2-43 years). Serum complement C4 level was decreased in all patients. All patients had low C1-esterase inhibitor (C1-INH) quantitative level (type 1 HAE). *SERPING1* gene sequencing could be carried out in 20 families. Of these, 11 were identified to have a pathogenic disease-causing variant in the *SERPING1* gene. While 2 of these families had a previously reported mutation, remaining 9 families had novel pathogenic variants in *SERPING1* gene. Because of non-availability of C1-INH therapy in India, all patients were given long-term prophylaxis (attenuated androgens or tranexamic acid (TA) or a combination of the 2). Life-threatening episodes of laryngeal edema were managed with fresh-frozen plasma (FPP) infusions. We recorded one disease-related mortality in our cohort. This happened in spite of long-term prophylaxis with stanozolol and TA.

Conclusions: We report largest single-center cohort of patients with HAE from India. Attenuated androgens, fibrinolytic agents, and FPP may be used for management of HAE in resource-limited settings.

KEYWORDS

attenuated androgens, C1 esterase inhibitor, children, hereditary angioedema, SERPING1, stanozolol, tranexamic acid

Abbreviations: C1-INH, C1 esterase inhibitor; FFP, fresh-frozen plasma; HAE, hereditary angioedema; SERPING1, serpin family G member 1; TA, tranexamic acid.

Edited by: Professor Marina Atanaskovic-Markovic

1 | INTRODUCTION

Hereditary angioedema (HAE) is an uncommon primary immunodeficiency, clinically characterized by recurrent, non-pruritic edema involving the face, extremities, genitalia, and upper airways.[1] Occasionally, this disease may manifest with pain abdomen due to edema involving gastrointestinal tract or an acute and life-threatening airway obstruction due to laryngeal edema.[2,3] The disease often starts in childhood, worsens at puberty, and may persist throughout life.[2,4–6] Detection of low serum levels of C1-esterase inhibitor (C1-INH) (quantitative and functional) along with low serum C4 is suggestive of a diagnosis of HAE.[5–7]

HAE is a rare genetic disorder most often caused by mutations in serpin family G member 1 (*SERPING1)* gene that leads to deficiency of C1-INH protein.[8] The disease is inherited in an autosomal dominant manner. However, spontaneous occurrences have also been reported in up to a quarter of patients[2] Epidemiologic studies suggest that the prevalence varies from 1:10,000 to 1.5:100,000.[9–12] HAE has been reported infrequently from developing countries.[13–21] There are no long-term follow-up studies and no data on genetics of HAE from India. In this study, we report our experience with HAE over last 2 decades. To the best of our knowledge, this would be one of the longest follow-up studies on pediatric HAE.

Key Message

We report the largest single-center cohort of type 1 hereditary angioedema (HAE) from India. Most patients had novel mutation in *SERPING1* gene. Clinical profile of patients in the present series was found to be similar to several previously reported series. Because of lack of availability of C1-INH therapy in India, patients were managed using attenuated androgens, tranexamic acid (TA), and fresh-frozen plasma (FPP). We recorded one disease-related mortality in our cohort. Results of this study suggest that the use of TA, stanozolol, and FPP may still be an effective treatment option for patients with type 1 HAE in resource-constrained settings.

2 | PATIENTS AND METHODS

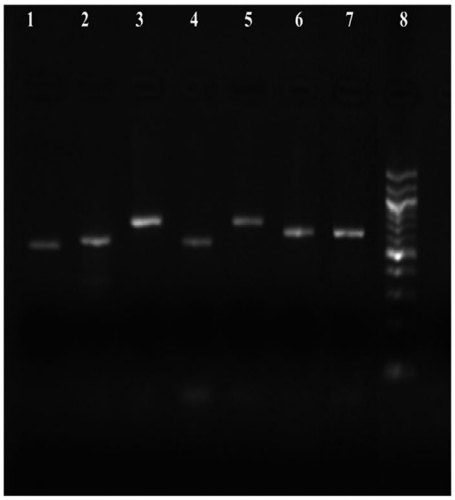
This study was carried out in the Allergy-Immunology Unit, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, North India. Our institute is a federally funded, not-for-profit tertiary care referral hospital for northwest India. The study included all patients diagnosed to have HAE between January 1996 and December 2019. Data were retrieved from medical records and entered in a predesigned pro forma. The study was approved by Institute Ethics Committee, and an informed consent was obtained from patients or their parents. Serum complement C4 was measured by end-point nephelometry using a semiautomated nephelometer (MININeph—The Binding Site). Functional C1-INH activity was assessed by MicroVue C1 inhibitor Plus enzyme immunoassay kit (Quidel). Our laboratory is regularly participating in an external quality assurance scheme, that is, UK National Quality Assurance Scheme for special proteins since 2010. Quantitative C1-INH was estimated using radial immunodiffusion method or semiautomated nephelometry. Patients were diagnosed to have HAE if they had characteristic clinical manifestations of disease with or without a suggestive family history with low C4 and either a low-quantitative C1-INH (type 1 HAE) or low-functional activity of C1-INH (type 2 HAE). Patients with suspected HAE but with normal quantitative and functional C1INH levels were not included in this analysis. Family members of patients with HAE for whom complete clinical details and laboratory data were not available were also excluded from this analysis.

Because of non-availability of recombinant or plasma-derived C1-INH therapy in India, stanozolol (2-4 mg/day), danazol (100-400 mg/day), or tranexamic acid [TA] (30-50 mg/kg/day) was used for long-term prophylaxis. The response was assessed clinically based on number and severity of attacks. For short-term prophylaxis during planned surgeries, stanozolol (2-4 mg/day) and fresh-frozen plasma, FFP (10 mL/kg) were used. Acute episodes of life-threatening laryngeal edema were managed using FFP (10 mL/kg).

Sanger sequencing for *SERPING1* gene:

TABLE 1 Primer sequence for the amplification of 8 exons of *SERPING1* gene: All oligonucleotides are designed in such a way that they anneal at 64°C temperature to the template and can easily amplify all 8 exons in 8 different reactions at same temperature conditions. For each exon, almost 100 bp of flanking intron sequence was also covered while designing the forward and reverse oligonucleotide

Exon no/primer name	Forward primer (5′–3′)	Reverse primer (5′–3′)	Product size (bp)
Exon 1	AGGTGAGCAATTTCCAAAAAGTTCATTC	TCCCAGGTGGAAGCAAGCCTATAGAG	533
Exon 2	GGAAAACAAAACAGAGGGAGGAGCCAG	TGGACAGGGTGGGATCTGTTTATTCAAC	555
Exon 3	AGATTACAGAGTCCCTGACTATCCCTC	CATGTTGGTCTCCACCTTCTTCATTGC	709
Exon 4	GAGAGAACACTTCCAGCTCAGATGATC	TCATCACTATTTTACTGTACCTGCCCG	548
Exons 5-6	AGAACCATAGAAAGCATGCTCACTCTC	TGTACCCCAAAATGATGGGACTACAGC	720
Exon 7	AGCGCTCAGAGAAATCAAATCACTTGC	GGGTTGCAGGACAAACTGAGATTATG	639
Exon 8	GGACAAAGGTCTCCATCAGCTGAG	GCAGAGAAAGTCATGGTCTGTCAGGT	602



Lane no	*SERPING1* exon (no)	Product size (bp)
1	*SERPING1* Exon 1	533
2	*SERPING1* Exon 2	555
3	*SERPING1* Exon 3	709
4	*SERPING1* Exon 4	548
5	*SERPING1* Exon 5,6	720
6	*SERPING1* Exon 7	639
7	*SERPING1* Exon 8	602
8	100 bp DNA ladder	

FIGURE 1 Optimization of the PCR conditions for the amplification of exons of *SERPING1* gene: Lane 1-7: PCR products of different exons (1, 2, 3, 4, 5-6, 7, 8) of *SERPING1* gene: Lane 8:100-bp DNA ladder

TABLE 2 Clinical manifestations of patients with HAE in the present study

Clinical manifestation	Proportions of patients (n = 32)
Swelling over face including lips and eyelid swelling (Figure 2)	32/32 (100%)
Swellings over extremities	28/32 (87.5%)
Swelling over genitalia	2/32 (6.2%)
Laryngeal edema	12/32 (37.5%)
Abdominal pain	10/32 (31.2%)
Erythema marginatum	4/32 (12.5%)
Family history	22/32 (68.7%)
Treatment (being given at the time of data analysis)	
Stanozolol alone	4/32 (12.5%)
Tranexamic acid alone	11/32 (34.3%)
Stanozolol and tranexamic acid	17/32 (53.1%)
Fresh-frozen plasma	12/32 (37.5%)

We started doing Sanger sequencing of SERPING*1* gene in our cohort of patients with HAE in 2018. For Sanger sequencing, 200 μl of EDTA blood was used. Genomic DNA was extracted using QIAamp DNA extraction kit as per the manufacturers' protocol (Qiagen). All exons of *SERPING1* gene were amplified using oligonucleotide primers as mentioned in Table 1 and Figure 1. These oligonucleotide primers were designed to cover exon/intron junctions of all exons. Each exon was amplified using polymerase chain reaction (PCR). The PCR product was checked on 1.5% of agarose gel electrophoresis followed by purification, and this purified product was used for Sanger Sequencing using the ABI Big Dye terminator kit and Agilent 2100 Bioanalyzer System. The sequencing data were analyzed using Finch TV and Codon code aligner software. In silico prediction analysis was used for all novel mutations detected in the *SERPING1* gene. The pathogenic nature of these variants was inferred using 3 free, online bioinformatics tools for prediction of functional effects of amino acid substitution in proteins, viz. Provean, PolyPhen-2, and FATTHM.

3 | RESULTS

In this study, we included 32 patients (21 male and 11 female) from 23 families who were diagnosed to have HAE. Median age at onset of symptoms was 6.25 years (range 1-25 years) and median age at diagnosis was 12 years (range 2-43 years) with median delay in diagnosis of 6.5 years (range 0-28 years). Clinical manifestations of patients in this study are detailed in Table 2. All patients had swelling over face (eyelids and/or lips) (Figure S1). Recurrent episodes of erythema marginatum preceding a flare of disease were noted in 4 patients. Although abdominal symptoms were noted in almost one-third of patients, only 1 patient presented with acute surgical abdomen and underwent exploratory laparotomy. No patient in this study had central nervous system complaints. Stress, exercise, and blunt trauma were the only identifiable triggers for flare of symptoms. However, most patients reported no definite trigger for their episodes. All patients had low serum complement C4 levels and low serum C1-INH levels. C1-INH activity was also low in all patients in who it was tested. Thus, all patients in the present study had type 1 HAE (C1-INH-HAE).

Most common differential diagnosis at presentation was allergic angioedema. Patients with HAE did not experience significant itching or redness, nor did they respond to antihistaminic drugs and/or corticosteroids.

SERPING1 gene sequencing could be carried out in 29 patients from 20 families till the time of this analysis. Of these, 17 patients from 11 families were found to have a pathogenic variant in the *SERPING1* gene, while no pathogenic variant was detected in 12 patients from 9 families. Most mutations in the *SERPING1* gene in our cohort were located in exon 7 and exon 8 (in 4 and 3 families, respectively). Missense mutations were most common and seen in 5/11 families while nonsense, frameshift, and splice-site mutations were seen in 2/11 families each (Figures 2 and 3). Nine out of these 11 families had a novel mutation while in remaining 2 families a previously reported mutation was identified. In addition, 20 benign polymorphisms in *SERPING1* gene were observed in 14 patients from 13 families (Table S1). Intron 6 polymorphism (c.1029 + 20A>G) was

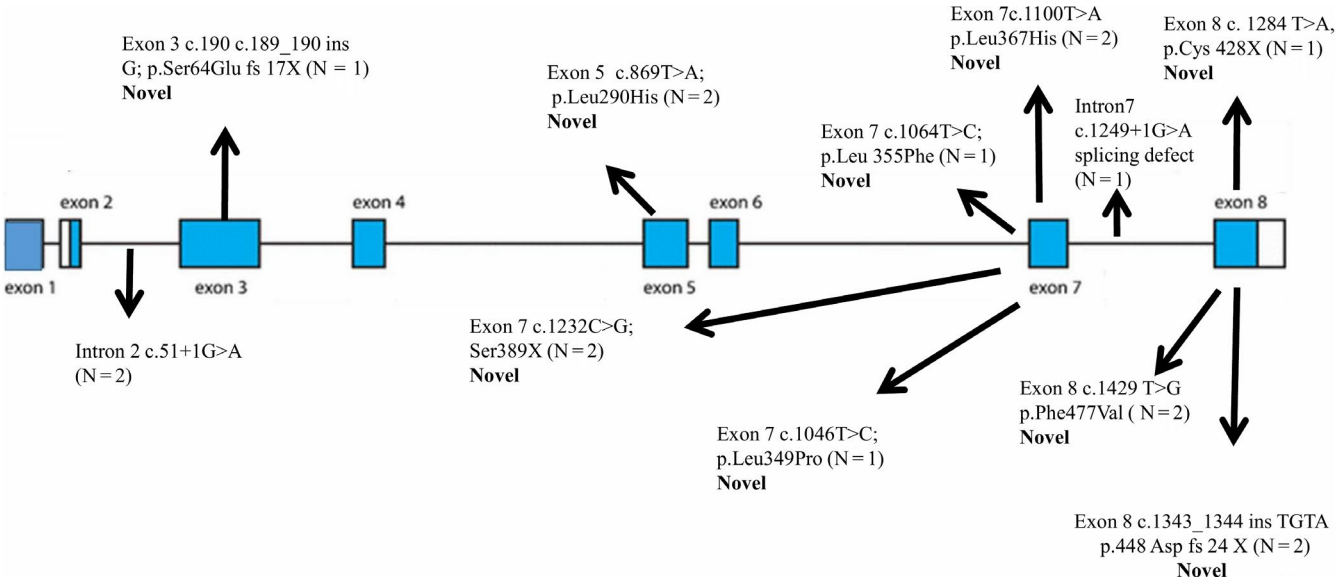


FIGURE 2 Distribution of mutations on *SERPING1* gene in the present study

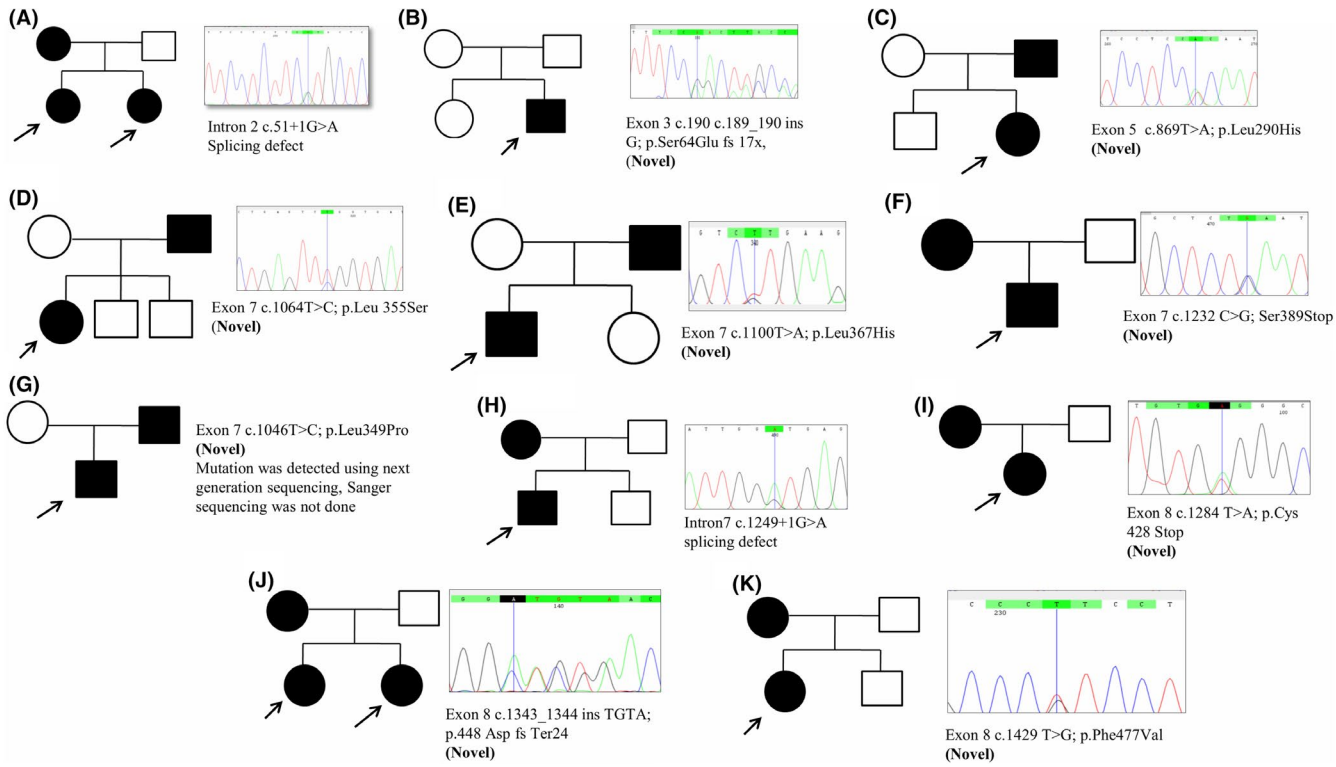


FIGURE 3 Pedigree charts of 11 families wherein a mutation was detected in SERPING1 gene along with their sequence chromatograms from each family

most common (in 6 patients) followed by exon 8 polymorphism (c.1438 G > A; p.Val480 Met) and intron 3 polymorphism (c.251-106 T > G) [in 4 patients each].

Most patients who were diagnosed prior to 2015 were initiated on stanozolol (2 mg/day) or danazol (100-400 mg/day). However, over last 4 years, patients were initiated on either a combination of stanozolol and TA or TA alone. Patients were initiated on stanozolol primarily based on clinical assessment of the senior author (SS). Factors taken into consideration included frequency and severity of attacks of angioedema and ease of access to healthcare facilities. Depending on the response, stanozolol was either discontinued after 6 months to 1 year or continued at a dose of 0.5-2 mg per day. Stanozolol had to be initiated in patients who failed to respond to TA alone (Table 2). Four patients who were initially given stanozolol and

TABLE 3 Side effect profile of patients with HAE who were given attenuated androgens before or during the puberty

S. no.	Current age (years), Gender	Anabolic androgen used and dose	Height gained during use of androgens	Final adult height/present height	Side effects[f]
1	25, F	Stanozolol (between 6-20 years of age): 1 mg/day × 22 months; 2 mg/day × 3 years; 1.5 mg/day × 8 years[a]	Accurate information not available	161 cm	Menstrual irregularities, hirsutism, oligomenorrhea
2	32, F	Stanozolol (between 12-28 years of age): 2 mg/day × 8 years[a]; 3 mg/day × 9 years; 1 mg/day × 3 months	Accurate information not available	163 cm	Acne, hirsutism, excessive weight gain, change in voice, menstrual irregularities, oligomenorrhea, hypertension
3	15, M	Stanozolol (between 4 and 11 years of age): 4 mg/day × 1 month; 2 mg/day × 7 years	Approximately 5.5 cm per year	165 cm	None
4	27, F	Danazol (50-100 mg per day for 3 years between 3 and 6 years of age);[a] Stanozolol (between 7 and 23 years of age): 4 mg/day × 4 months; 3 mg/day × 1 year; 4 mg/day × 4 years;[a] 4 mg/day × 8 months; 2 mg/day × 1 month; 1 mg/day × 1 month; 0.5 mg/day × 1 month	Accurate information not available	165	Menstrual irregularities, oligomenorrhea
5	16, F[b]	Stanozolol (between 9 and 16 years of age): 4 mg/day × 22 months; 2 mg/day × 26 months; 0.75 mg/day × 11 months; 1 mg/day × 24 months[a]	Approximately 5 cm per year	162.5 cm at 14 years of age	Hoarseness of voice, hirsutism, acanthosis nigricans, primary amenorrhea, excessive weight gain
6	19, M	Stanozolol (between 12 and 14 years of age): 2 mg/day × 15 months; Danazol (between 14 and 16 years of age): 100 mg/day × 2 years	Approximately 6 cm per year	192 cm	None
7	8, F	Stanozolol (between 3 and 8 years of age): 0.5 mg/day × 4.5 years	Approximately 9 cm per year	140 cm	Acne, hirsutism, precocious puberty
8	17, M[c]	Stanozolol (between 13 and 15 years of age): 8 mg/day × 1 month; 6 mg/day × 1 month; 3 mg/day × 4 months; 2 mg/day × 14 months; 1 mg/day × 7 months; 0.5 mg/day × 1 month	Approximately 6 cm per year	Accurate information not available	None
9	14, M[d]	Stanozolol (between 10 and 14 years of age): 4 mg/day × 3 years	Approximately 7.5 cm per year	Accurate information not available	None
10	12, M	Stanozolol (between 11 and 12 years of age): 3 mg/day × 4 months (intermittent doses afterward)	Approximately 6 cm per year	168 cm	Aggressive behavior, excessive weight gain, excess hair growth, acne
11	16, M	Stanozolol (between 14 and 16 years of age): 2 mg/day × 1.5 years	Approximately 6 cm per year	153 cm	Excessive weight gain

(Continues)

TABLE 3 (Continued)

S. no.	Current age (years), Gender	Anabolic androgen used and dose	Height gained during use of androgens	Final adult height/present height	Side effects[f]
12	12, F	Stanozolol (between 11 and 12 years of age): 1 mg/day × 1 year	Approximately 6 cm per year	153 cm	Excessive weight gain Onset of puberty between 11 and 12 years of age (while on stanozolol)
13	13.5, M	Stanozolol (between 12 and 13 years of age): 2 mg/day × 1 year	Approximately 7 cm per year	153 cm	Excessive weight gain
14	9.5, M	Stanozolol (between 8.5 and 9.5 years of age): 2 mg/day × 5 months; 1 mg/day × 5 months	Approximately 8 cm in 10 months	149 cm	Excessive weight gain
15	9.5, M	Stanozolol (between 8 and 9 years of age): 2 mg/day × 2 months; 1 mg/day × 2 months	Approximately 6 cm per year	152 cm	Aggressive behavior and frequent penile erection[e]

[a]Inadequate compliance during this time and missed intermittent doses. However, exact records are not available.
[b]Died at 16 years of age due to laryngeal edema.
[c]Died at 17 years of age because of road traffic accident.
[d]Lost to follow-up at 14 years of age.
[e]Distressing but no long-term consequences.
[f]Biochemical assays (liver function tests and lipid profile) were not carried out routinely; ultrasound scans for liver were not performed routinely.

TA stopped taking treatment in the third decade as the severity and frequency of attacks had decreased.

Short-term prophylaxis with FFP and stanozolol was used successfully in two patients prior to surgery. Both patients had uneventful perioperative period.

Acute therapy was used for episodes of laryngeal edema only. FFP (10 mL/kg, maximum 2 units) infusion was used for 15 such episodes. The interval between onset of laryngeal edema and administration of FFP was not reported in all patients but it was found to be variable (between 4 and 10 hours). All patients showed prompt response to FFP and symptoms resolved within 1 hour.

Several side effects of attenuated androgens were reported when they were used in prepubertal age group (Table 3). These included the following: menstrual irregularities, weight gain, acne, hoarseness of voice, hirsutism, acanthosis nigricans, and aggressive behavior. One patient also developed hypertension. Most of these side effects were reversible. Presence of side effects necessitated temporary discontinuation of medications. None of the patients treated with attenuated androgens showed overt hepatic or hematological abnormalities. However, we did not perform regular assay of liver functions. Hepatic ultrasound scans were also not performed (Tables 3 and 4). None of the patients on long-term attenuated androgens had significant growth arrest. Other than one patient who had 2 spontaneous abortions during the first trimester while she was being continued on TA prophylaxis, no side effects related to TA therapy were reported in this study.

One patient in our cohort died during an exacerbation. She was taking stanozolol and TA as long-term prophylaxis. She developed an acute episode of laryngeal edema in the evening at home. Parents reported no peripheral edema at that time. She collapsed within 30 minutes of onset of respiratory distress before her parents could access FFP infusion and she died on way to hospital. Another patient in this study died due to a road traffic accident. In addition, at least 3 patients could recall the death of one family member from choking episode in the recent past.

Mean follow-up period in this study is 57 months (±81.5, range 4-288). The total follow-up period of the entire cohort is 1944 patient-months.

4 | DISCUSSION

HAE is an uncommon autosomal dominant disorder characterized by recurrent episodes of subcutaneous edema, reduced complement C4, and low antigenic and/or functional levels of C1-INH. HAE is a potentially life-threatening medical condition. Depending on the C1-INH antigenic and functional levels, HAE has been classified into three different types.[7] In majority (80%-85%), there is a reduction of both antigen and functional levels of C1-INH protein (type I HAE), and in 15%-20% patients, C1-INH antigen levels are normal or elevated but it is dysfunctional (type II HAE). A rare form of hereditary angioedema (HAE nlC1-INH) is characterized by normal levels and function of C1-INH protein. HAE nlC1-INH is most commonly caused by mutation of

TABLE 4 Side effect profile of patients with HAE who were given attenuated androgens after puberty

S. no.	Current age (years), Gender	Anabolic androgen used and dose	Final adult height	Side effects[a]
1	41, M	Danazol 100 mg (between 35 and 41 years of age)—given intermittently	165 cm	None
2	41, M	Stanozolol 2 mg/day × 1 year (between 40 and 41 years of age)	Accurate information not available	None
3	27, M	Stanozolol 2 mg alternate day × 1 year (between 26 and 27 years of age) Infrequent doses of stanozolol and danazol (maximum 50 mg) were also taken prior to this[b]	187 cm	None
4	60, M	Danazol 100-400 mg/day (between 35 and 40 years of age)[b] Stanozolol 1 mg per day × 1 year (between 59 and 60 years of age) Infrequent doses of stanozolol were also taken prior to this	168 cm	None
5	24, F	Stanozolol 2 mg per day × 1 year (between 23 and 24 years of age)	158 cm	None, no menstrual irregularities

[a]Biochemical assays (liver function tests and lipid profile) were not carried out routinely; ultrasound scans for liver were not performed routinely.

[b]Danazol was prescribed in the Department of Dermatology before referring to our clinic for evaluation.

coagulation factor XII (*F12*) gene. Recent advances in the genetic studies have identified some new genes that are associated with HAE nlC1-INH. These include mutations in *angiopoietin 1* gene (HAE-ANGPT1), *plasminogen* gene (HAE-PLG), and *Kininogen-1* gene.[8,22–25] Acquired angioedema (AAE-C1-INH) has mostly been reported in association with drugs, autoimmune diseases, and B-cell lymphoproliferative disorders.[26] Patients with AAE have older age at onset (4th or 5th decades of life). These patients have low levels or abnormal function of C1-INH and low levels of C1q. The present study, however, focused on patients with type 1 HAE (C1-INH-HAE), and patients who had normal C1-INH antigen level were excluded from the study.

Published literature on HAE from developing countries is very limited.[13–19,27–29] To the best of our knowledge, no long-term follow-up studies are available from India, especially in children. Moreover, there are limited data on genetic profile of patients with HAE from developing countries including India. Studies conducted in China[27] and Japan[30] reported that the incidence of HAE in Asian countries is less as compared to studies from Latin American and Western countries such as Brazil,[31] Hungary,[32] and Denmark[33,34] However, precise epidemiologic figures are not available.[35] Table 5 shows an overview of published studies on type 1 and 2 HAE including few pediatric studies.[12,27,30–34,36–46]

Diagnosis of HAE can be easily made from the characteristic edema and is supported by a positive family history. Low serum C4 level is a cost-effective method of screening for HAE.[2,3] However, sensitivity of low C4 in diagnosing HAE is only 81%.[47] In our cohort, the characteristic swelling was present in all patients and low C4 levels were detected in all. It has, however, been reported that C4 levels may occasionally be normal in HAE.[2,36] Assessment of serum C1-INH level (antigenic and functional) helps in establishing an accurate diagnosis. All patients in the present study had low C1-INH antigen levels.

Median age at onset of symptoms was 6.25 years in the present study which is comparable with several other previously published studies (Table 5). Median age at time of diagnosis was 12 years with median delay in diagnosis of 6.5 years. This is largely because of lack of awareness among primary care physicians and most patients were initially managed elsewhere as allergic angioedema.

No definite triggers were discernible in most patients in the cohort except few patients who identified blunt trauma, psychosocial stress, and exercise as potential triggers. Frequency of attacks was discernibly less during pregnancy in two patients in our study. One of these two patients was continued on TA prophylaxis and she had an uneventful pregnancy. The other patient experienced 2 first trimester abortions while she was on TA prophylaxis even though she had no episodes of angioedema during both pregnancies. Pregnancy has variable effects on the clinical course of HAE.[48–50] Attenuated androgens are contraindicated during pregnancy and plasma-derived

TABLE 5 Review of literature and comparison of present study with previously published studies

	Country	No. of patient	Age at onset, years (range)	Age at diagnosis, years (range)	Family history	Trigger
Roche et al (42)	Spain (multicenter)	444	Mean 12.6 (0-65)	Mean 24.9 (0-78)	417 (94%)	Not stated
Grumach et al (31)	Brazil (multicenter)	210	Median 6.5; (1 month-64 years)	Mean 21 ± 14	163/210	111 patients
Farkas (32)	Hungary (single center)	49	Median 6.6	Median 6 (4-11)	41/49	Present
Bygum et al (33)	Denmark (multicenter)	59	Median 7 (1-30)	Not stated	All	Not stated
Bork et al (34)	Germany (single center)	209	Mean 11.2 ± 7.7	Not stated	188/209	Absent
Xu et al (27)	China (multicenter)	153	Mean 21.25	Not stated	Not stated	Not stated
Psarros et al (44)	Greece (multicenter)	116	Median: 10 (1-57)	Not stated	Not stated	Present
Ohsawa et al (30)	Japan (multicenter)	171	Mean 24.2(4-68)	Mean 37.1(2-80)	131/171	Not stated
Aabom et al (36)	Denmark (multicenter)	22	Median 4(1-11)	Not stated	19/22	Not stated
Lumry et al (37)	USA (multicenter)	9	Not stated	Not stated	Not stated	Not stated
Christiansen et al (38)	USA (multicenter)	581	Median 11 (6-15)	Median 19 (12-28)	Not stated	Not stated
Nanda et al (39)	USA (single center)	21	Median 5.7 (IQR:5-9)	Median 5 (IQR:4-8)	18/21	Present
Zanichelli et al (12)	Italy (multicenter)	983	Not stated	Median: 26 (IQR: 13-41)	Not stated	Not stated
Nordenfelt et al (45)	Sweden [a](multicenter)	146	Median: 12 (0-50)	Median: 22 years (1-81)	87%	Present
Steiner et al (46)	Switzerland (multicenter)	104	Mean 11 ± 8.2	Mean: 19.5 ± 14.1	Not stated	Present
Engel-Yeger et al (40)[b]	Israel, Hungary	98	Not stated	Not stated	Not stated	Not stated
Busse et al (41)[c]	Multination	39	Not stated	Not stated	Not stated	Present
Karadža-Lapić et al (43)	Croatia (multicenter)	9	Range: 1-15 years	Not stated	100%	Not stated
Present study	India (single center)	32	Median 6.25 (1-25)	Median 12 (2-43)	22/32 (68.7%)	Yes[d]

Note: Abbreviations EACA, epsilon aminocaproic acid; IQR, interquartile range; LTP, long-term prophylaxis; TA, tranexamic acid.

[a]A written questionnaire followed by a structured telephone interview.

[b]This study was aimed to assess the quality of life of children with hereditary angioedema.

[c]This study was aimed to assess the safety of C1-INH concentrate in hereditary angioedema.

[d]Psychosocial stress, exercise, and blunt trauma.

C1-INH and TA are considered safe. Mental stress has also been reported to be an important trigger in these patients.[7,51]

There can be substantial inter-individual variation in onset of symptoms of HAE, duration of symptoms, frequency of attacks, and severity of symptoms. These differences can exist within members of the same family as was the case in several of our patients. In the Hungarian cohort, the clinical attacks were found to be more severe in children who had earlier age of disease onset.[32]

Subcutaneous edema	Abdominal symptoms	Laryngeal edema	C4	C1-INH	Follow-up
Not stated	Not stated	47 (10.6%)	Not stated	Not stated	Not stated
170 patients	114 patients	32	Median 5.95; range, 0.2-33 mg/dl (N:10-40 mg/dl)	Median 8.9; range 0.05-38 mg/dl (N: 21-40 mg/dl)	Not stated
27	3	23	Not stated	Not stated	Followed up till 18 years of age
56	56	33	Not stated	Mean function 26% (range, 20%-46%)	Not stated
209	195	50	Mean: 0.09 ± 0.047 g/L (N: 0.20-0.50)	Mean: 0.29 ± 0.16 g/L (N:0.15-0.35), Activity: 16.9 ± 9.6 (N:70%-130%)	5736 patient years
83.54%	34.17%	Not stated	Not stated	Not stated	Not stated
98.7%	88%	60%	Mean C4 (7.34 and 5 in type 1 and II HAE, respectively, N = 12-72)	Mean antigenic C1-INH 8.4 and 51.6 in type 1 and II HAE respectively (N = 15-35 mg/dL) Mean functional C1-INH 44.3 and 50.5 in type 1 and II HAE respectively (N > 68%)	Not stated
Not stated	5	16	Not stated	Assayed in 111 patients, Low levels in 99, Normal level with decreased activity in 9, Normal level and activity in 3	Not stated
11/14 (79%)	14/14 (100%)	4/14 (29%)	Normal or near-normal values in 7/18 patients	Assayed in 18/22, Low levels/ function in all	Observation period of 45 months
6/9 (67%)	7/9 (78%)	2/9 (22%)	Not stated	Not stated	median duration > 3.4 years
Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
11/15 (73%)	14/15 (93%)	4/15 (27%)	Not stated	Median: 6.0 (IQR: 4.75-8.75)	Not stated
Not stated	Not stated	Not stated	C4 ≤ 50% in 96%	Functional C1INH ≤ 50% in 99% and antigen C1INH ≤ 50% in 99% of type 1 HAE	Not stated
82%	78%	27%	Not stated	Not stated	Not stated
Not stated	65%	15%	Not stated	Not stated	Not stated
Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
47%-66%	70%-100%	6%-28%	Not stated	Not stated	Not stated
55%	12%	12%	Low in all	Low-quantitative level in all, normal functional activity in 2/9	Not stated
All	10/32 (31.2%)	12/32 (37.5%)	Low in all	Low-quantitative levels and/or functional activity in all	Mean 57 months (total 1944 patient-months)

Recurrent abdominal pain may be seen in 30%-100% of patients with HAE.[27,31,52] It may be the initial presenting symptom in 40%-80% of children.[16,53] In the presented study, one-third of all patients reported having gastrointestinal symptoms. Patients with predominant abdominal symptoms may inadvertently be subjected to exploratory laparotomy.[30] In one study, three patients presented with edematous abdominal attacks as initial symptoms.[32] One patient in the present cohort had a history of exploratory

laparotomy for acute surgical abdomen, several years before he was diagnosed to have HAE.

Erythema marginatum could be an early manifestation of HAE and may precede a disease flare. It may easily be confused with urticaria and is more commonly reported in children and with type 1 and 2 HAE.[7,54] Erythema marginatum was seen in three patients in the present series.

In children, the only recommended drugs for management of acute episode of HAE are C1-INH concentrate.[7] Solvent detergent-treated plasma (SDP) or FFP may be considered when C1-INH therapy is not available.[7] As C1-INH concentrate is not readily available commercially in our country, we had to administer FFP in our patients with laryngeal edema and patients showed prompt resolution of symptoms. FFP may be considered as acute therapy in countries where C1-INH therapy and icatibant are not easily available.[21] However, there are safety concerns with use of FFP. These include risk of viral transmission (such as hepatitis B, human immunodeficiency virus, and hepatitis C), allergic reactions, volume overload, transfusion-associated lung injury, and a paradoxical flare of an acute attack (because FFP itself may contain contact proteins).[21,55]

Patients and their parents were explained about need of long-term prophylaxis and available treatment options. All patients opted for long-term prophylaxis as effective on-demand treatment is not available in India and access to FFP in emergency situations may not always be possible. TA has favorable side effect profile when compared to attenuated androgens. However, long-term use of attenuated androgens may be considered under careful monitoring.[7,51] In India, we do not have access to plasma-derived C1-INH therapy and icatibant. Therefore, we considered attenuated androgens (stanozolol) as the agent of choice for long-term prophylaxis of HAE. Most patients in our cohort showed reduction in frequency and severity of HAE attacks with stanozolol prophylaxis. However, few patients continued to have disease flares, even severe airway obstruction requiring plasma therapy and one patient died while they were taking stanozolol prophylaxis. It has been observed that attenuated androgens are more effective than TA.[7] We have been using TA more frequently since 2015. It is now our preferred treatment modality in most patients because of its better side effect profile.

Patients with HAE are prone to develop disease flares and occasionally life-threatening laryngeal edema during surgical procedures especially dental surgeries.[7] Plasma-derived C1-INH therapy is recommended as short-term prophylaxis during these procedures. Use of attenuated androgens and FFP has also been suggested if C1-INH is not available.[56,57] We successfully used stanozolol and FFP for short-term prophylaxis in 2 patients in the present series.

Genetic profile of patients with HAE has been studied for the first time in India. We found mutations in the *SERPING1* gene in 11 out of 20 families who were screened. Nine of these 11 families had a novel pathogenic variant in the *SERPING1* gene. Missense mutations in exon 7 and 8 were the most common mutations in our cohort. Mutation spectrum in *SERPING1* gene is quite heterogeneous and more than 450 mutations spread over the entire gene have been reported so far.[33,58–61] Missense mutations have been reported to be the most common mutations in *SERPING1* gene.[8,62–64] while some populations have reported that nonsense or frameshift mutations are most common.[33] Missense mutations in exon 8 have also been reported to be the most common mutation in certain populations.[62,63,65] Few authors have also reported a genotype-phenotype correlation and have shown that nonsense, frameshift, and deletion mutations are associated with a more severe disease phenotype.[55,66] However, several other authors have reported no genotype-phenotype correlation and have suggested that polymorphisms in bradykinin receptor or contact system proteins may be responsible for this apparent phenotypic heterogeneity.[33,62] In the present study, we observed no significant genotype-phenotype correlation but our numbers are decidedly small. Family members with same mutations were noted to have wide variations in age of symptom onset and disease severity thereby suggesting phenotypic heterogeneity.[8]

We performed Sanger sequencing for all 8 exons of SERPING1 gene. However, nine families (45%) were not found to have any pathogenic variant. All these families had characteristic clinical manifestations of HAE with low C4 and low C1-INH. All except 2 of these patients also had suggestive family history. Proportion of patients who are not found to have mutation in SERPING1 gene should normally be 5%-10% but this figure was relatively high in our study. It is possible that we have missed mutations in promoter region and deep-intronic regions of the *SERPING1* gene and large mutations in these patients. Recently, a deep-intronic novel pseudoexon activating mutation in intron 6 of *SERPING1* gene has been reported in a family with HAE.[67] Therefore, some of the patients with HAE in this study may have this deep-intronic mutation or a variant in promoter region of the gene. This would warrant more detailed genetic testing for these families.

5 | CONCLUSION

This is the first study on long-term follow-up of HAE from India. The major strength of the study is its duration of follow-up (1944 patient-months) which is one of the longest reported so far in children. Genetic profile of HAE in India is being reported for the first time. In resource-constraint settings where C1-INH concentrate is not available, FFP may be an effective option for acute management. Though recent guidelines for management of HAE in children recommend the use of C1-INH for long-term prophylaxis, our experience suggests that in developing countries and resource-limited settings, attenuated androgens and fibrinolytic agents may also have a role in management. In the present situation, when several options are available and more effective options are being explored for long-term prophylaxis and for acute management of HAE, all attempts must be made to avail these medications for patients. The use of TA, attenuated androgens, and FFP may not be advocated for patients with HAE in developed countries who have access to modern treatments.

However, such therapies for HAE may not be available in several developing countries as is also the case in India at present. Our experience suggests that the use of TA, stanozolol, and FFP may still be an effective treatment option for patients with HAE in these countries. Side effects of androgens on children seem very frequent and severe. Clearly, very difficult risk/benefit choices have had to be made. Safer accessible treatments for all, but in particular for children with HAE in resource-poor countries such as India are urgently required.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ankur Kumar Jindal: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Amit Rawat:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (supporting); Investigation (lead); Methodology (supporting); Project administration (supporting); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal). **Anit Kaur:** Data curation (supporting); Formal analysis (supporting); Investigation (equal); Writing-original draft (supporting); Writing-review & editing (supporting). **Dhrubajyoti Sharma:** Formal analysis (supporting); Investigation (supporting); Writing-original draft (equal); Writing-review & editing (equal). **Deepti Suri:** Conceptualization (equal); Investigation (equal); Supervision (equal); Writing-original draft (equal). **Anju Gupta:** Conceptualization (equal); Data curation (equal); Supervision (equal); Writing-review & editing (equal). **Ravinder Garg:** Data curation (equal); Investigation (equal); Supervision (equal). **Sunil Dogra:** Data curation (equal); Formal analysis (equal); Supervision (equal); Writing-review & editing (equal). **Biman Saikia:** Data curation (equal); Formal analysis (equal); Investigation (equal); Supervision (equal); Writing-review & editing (equal). **Ranjana Minz:** Data curation (equal); Formal analysis (equal); Supervision (equal); Writing-review & editing (equal). **Surjit Singh:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Supervision (lead); Writing-original draft (equal); Writing-review & editing (lead).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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