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Delay in diagnosis is the most important proximate reason for mortality in hereditary angio-oedema: our experience at Chandigarh, India

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Abstract

Background Hereditary angio-oedema (HAE) is a rare autosomal dominant disorder characterized clinically by recurrent episodes of non-pruritic subcutaneous and/or submucosal oedema. Laryngeal oedema is the commonest cause of mortality in patients with HAE. Prior to the availability of first-line treatment options for the management of HAE, mortality was as high as 30%. Mortality has significantly declined in countries where first-line treatment options are available and patients can access these therapies. There is a paucity of literature on the outcomes of patients with HAE in developing countries where availability of and access to first-line treatment options are still a challenge.

Objectives To report our experience on mortality in patients with HAE and to report factors associated with the death of these patients.

Methods We carried out a record review of all patients diagnosed with HAE between January 1996 and August 2022. Families with HAE who had reported the death of at least one family member/relative from laryngeal oedema were studied in detail.

Results Of the 65 families (170 patients) registered in the clinic, 16 families reported the death of at least one family member/relative from laryngeal oedema (total of 36 deaths). Of these 16 families, 14 reported that 1 or more family members had experienced at least 1 attack of laryngeal oedema. One patient died during follow-up when she was taking long-term prophylaxis with stanozolol and tranexamic acid, while the remaining 35 patients were not diagnosed with HAE at the time of their death. At the time of death of all 36 patients, at least 1 other family member had symptoms suggestive of HAE, but the diagnosis was not established for the family.

Conclusions To our knowledge, this is the largest single-centre cohort of patients with HAE in India reporting mortality data and factors associated with death in these families. The delay in diagnosis is the most important reason for mortality.

What is already known about this topic?

- Mortality of hereditary angio-oedema (HAE) has decreased significantly with first-line medications in developed countries.
- However, studies are scarce in resource-limited settings where first-line medications are unavailable.

What does this study add?

- Delay in diagnosis of HAE and lack of access to first-line treatment options were the two important factors responsible for mortality in patients with HAE in our settings.
- Availability of first-line medications at an affordable cost is the need of the hour, along with increasing awareness of HAE among healthcare workers, to avoid delay in diagnosis of these patients.

Hereditary angio-oedema (HAE) is a rare autosomal dominant disorder characterized clinically by recurrent episodes of nonpruritic subcutaneous and/or submucosal oedema.[1] The two more common types of HAE are type 1, with a

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deficiency of plasma protease C1 inhibitor (C1Inh) and type 2, with dysfunctional C1Inh. These types are caused by mutations in the *SERPING1* gene, which encodes C1Inh. Rarer types include HAE with normal C1Inh, which arise from mutations in *F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF* and *HS3ST1*.

Patients with HAE present with swelling involving the face, hands, feet and genitalia. Those with involvement of the gastrointestinal tract may present with excruciating abdominal pain, abdominal distension, vomiting and sometimes diarrhoea.[2] Laryngeal oedema is a life-threatening complication of HAE, and more than 50% of patients develop at least one episode of laryngeal oedema during their life.[3] Prior to the availability of first-line treatment options for HAE, mortality used to be approximately 30%.[4] In a recent review by Minafra *et al.*, studies that reported deaths in patients with HAE were analysed in detail. Of the 3292 patients with HAE reported in these studies, 411 patients had died from laryngeal oedema,[3] in addition to 103 close relatives of these patients. In a previous study from our centre, 32 patients were included. Of these, one patient died from laryngeal oedema, while three families reported the death of at least one of the relatives due to laryngeal oedema. Diagnosis of HAE was not established in the relatives prior to death.[5]

Mortality has significantly declined in countries where first-line treatment options are available and patients can access these therapies.[1,6] However, there is a paucity of literature on outcomes of patients with HAE in developing countries where availability of and access to first-line treatment options remain a challenge.[5] In India, none of the first-line treatment options were available until September 2022. At present, two intravenous preparations of plasma-derived C1Inh concentrate are available.

In this study, we report our experience on mortality in patients with HAE and their relatives who had died prior to the availability of any first-line treatment options. We also report various factors that might have been associated with death in these patients.

Patients and methods

Patient record review and pedigree chart

We carried out a record review of all patients diagnosed with HAE from the Pediatric Allergy Immunology Clinic of the Postgraduate Institute of Medical Education and Research, India, between January 1996 and December 2022. Families who had reported death due to laryngeal oedema of at least one family member/relative were studied in detail. A pedigree chart for each family was prepared, and details of all family members that could be recalled by the index patients/parents were included. We also contacted the close relatives of these families to obtain additional details of those family members/relatives.

Diagnosis of hereditary angio-oedema and molecular analysis

Diagnosis of HAE in the index case was based on the presence of characteristic clinical manifestations with low C4 and low quantitative C1Inh levels (type 1 HAE). Molecular analysis in all families was carried out using in-house Sanger sequencing, or targeted next-generation sequencing and whole exome sequencing. Because tests to assess the functional activity of C1Inh were not available, diagnosis of type 2 HAE was considered if patients had low C4 levels with normal/high C1Inh levels and a pathogenic variant in *SERPING1*.

Data analysis

Clinical details, laboratory investigations and details of molecular analyses of these families were recorded in a predesigned Excel spreadsheet. Analyses were carried out to identify various factors that might have been associated with the death.

Results

Characteristics of patients and families

During the study period, of the 65 families (170 patients) registered in the clinic, 16 families reported the death of at least one family member/relative from laryngeal oedema (a total of 36 deaths). Figures 1–4 show the respective pedigree charts of these 16 families. Of the 16 families, 13 had type 1 HAE and 3 had type 2 HAE. Age at death was known in 31 patients; their median age was 38 years (range 17–55). Except for one patient who died during follow-up (Figure 5), diagnosis was not established prior to death in any of them. At the time of death of these patients, at least one other family member/relative had clinical manifestations suggestive of HAE (Figures 1–4). However, the diagnosis could not be established despite there being a strong family history of similar illness. For most family members/relatives who died, this was apparently the first appreciable episode of swelling. However, because of possible recall bias, this observation remains conjectural.

Of the 16 families, 14 had 1 or more family members who had experienced at least 1 attack of laryngeal oedema. In the remaining two families, none of the other family members had experienced an episode of laryngeal oedema. Abdominal involvement and tongue swelling in at least 1 family member were reported in 10 and 6 families, respectively (Table 1).

In this cohort, one patient died during follow-up, a 17-year-old girl who was diagnosed with HAE at the age of 10 years. She was on long-term prophylaxis with stanozolol and tranexamic acid. However, she was not compliant with the therapy because of adverse effects (amenorrhoea and hirsutism). She developed an acute episode of laryngeal oedema and died on her way to the hospital.[5]

Analysis of factors associated with mortality in families with hereditary angio-oedema

We tried to analyse various factors that might have been associated with risk of death in families with HAE. We compared clinical manifestations between families who reported death due to laryngeal oedema with families who reported no death (Table 1). It was observed that the type of HAE and presence of laryngeal oedema, abdominal symptoms and tongue swelling in at least one family member were not

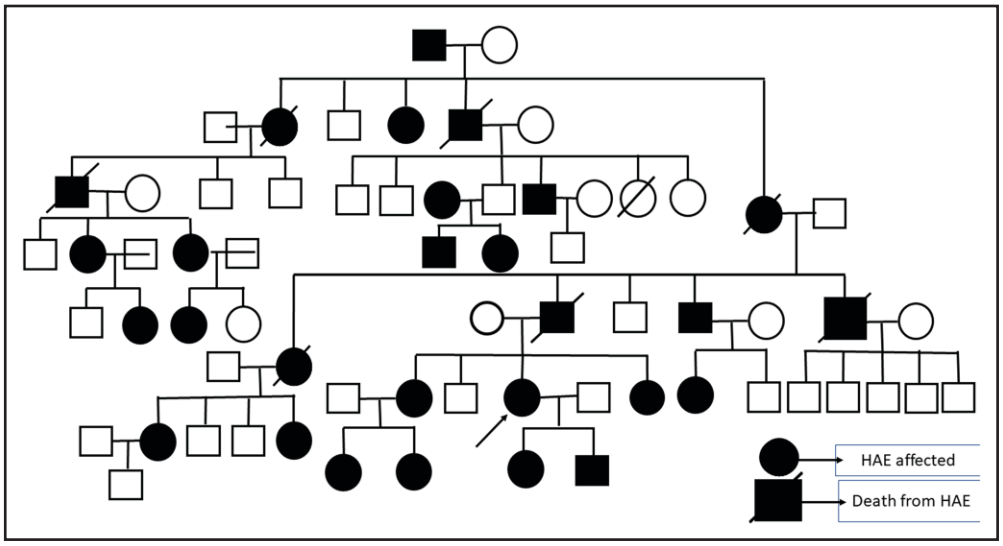

Figure 1 Pedigree of family 1. HAE, hereditary angio-oedema.

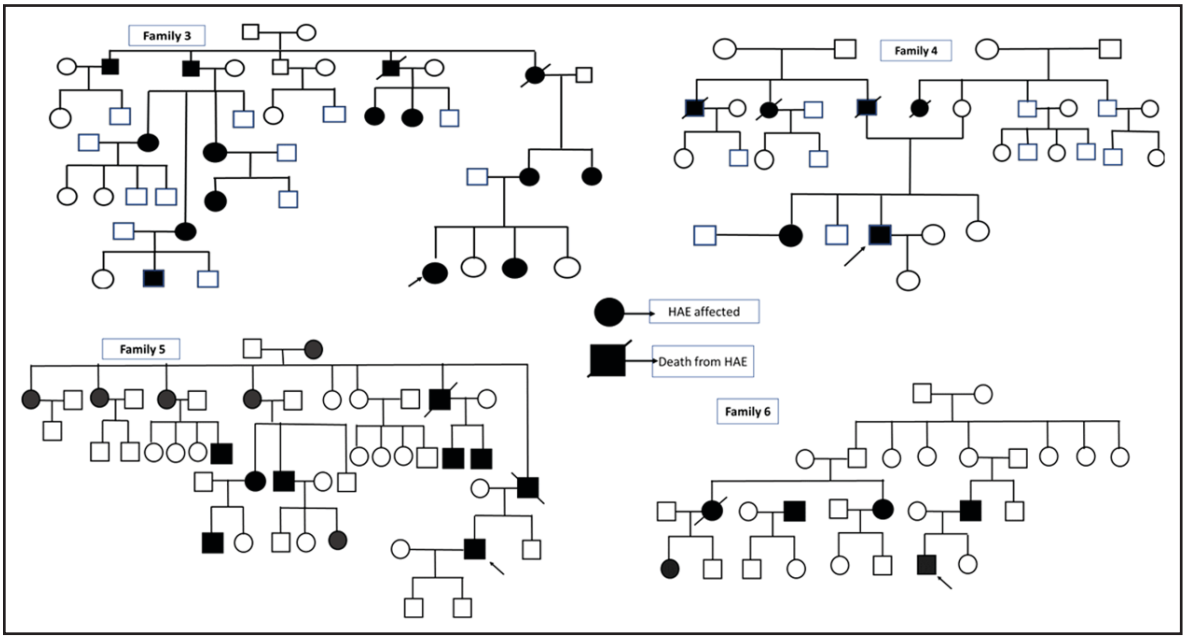

Figure 2 Pedigree of families 3–6. HAE, hereditary angio-oedema.

significantly different between the two groups. There was also no significant difference in the type of molecular variant (missense mutation or any other variant in *SERPING1*) in these two groups.

We additionally compared the clinical manifestations between patients who reported the death of at least one family member with those patients reporting no deaths in their family (Table 2). There was no significant difference in clinical features between the two groups.

Discussion

In this study, we report 16 families with HAE in which at least one of the family members had died from laryngeal oedema (in total, 36 deaths). The diagnosis of HAE prior to death in these patients was not established, except in one. Other than delays in diagnosis and lack of access to first-line treatment options, none of the other factors appeared to be a significant risk for death in these patients.

In the very first published report on HAE by Osler in 1888, two family members had died from laryngeal oedema.[7] Before the availability of first-line treatment options, the death rate due to HAE was high.[4,8,9] This has decreased significantly in developed countries because of an increase in awareness, and availability of and access to first-line treatment options.[10]

The recent review by Minafra *et al.* included a total of 23 studies for analysis. The authors observed that of the 3292 patients with HAE reported in these studies, 411

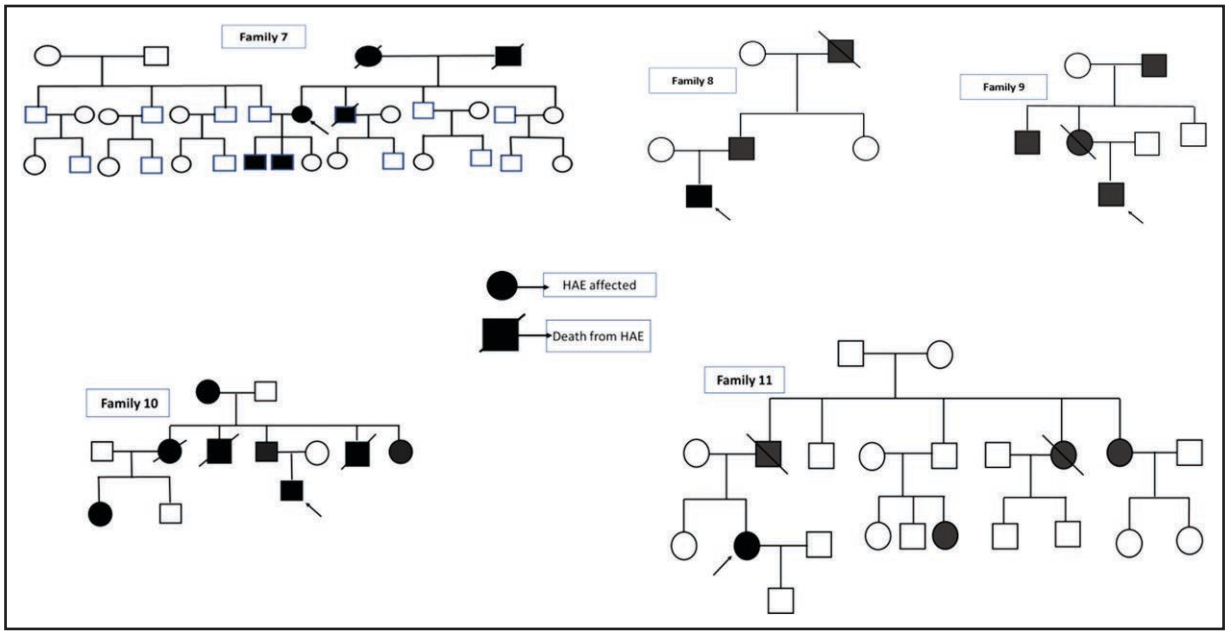

Figure 3 Pedigree of families 7–11. HAE, hereditary angio-oedema.

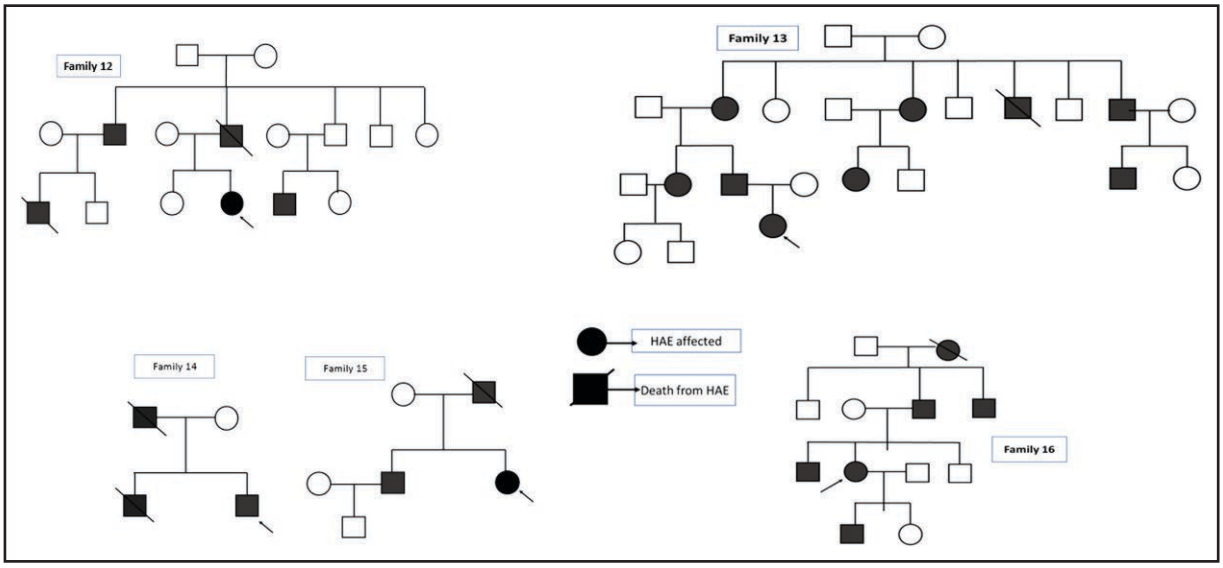

Figure 4 Pedigree of families 12–16. HAE, hereditary angio-oedema.

patients had died from laryngeal oedema. In addition, 103 close relatives of these patients had also died likely from HAE.[3] It was also noted that the time between onset of laryngeal oedema and death was highly variable (10 min to more than 24 h). Further analysis showed 1 death per 20 patients and among relatives 1 death per 7.4 patients.[3] Barbosa *et al.* from Brazil reported no deaths among their cohort of patients with HAE, but 29% of their patients reported deaths of one or more family members.[11] In the present study, we observed the death of 1 of 170 patients diagnosed with HAE. On the other hand, of these 65 families (170 patients), 16 families (25%) reported the death from HAE of 36 family members/relatives (1 family member death per 4.9 patients).

The mean age at death reported in three studies was 39, 40.8 and 46 years, respectively.[10,12,13] In the present study, median age at death was 38 years (range 17–55) (Table 3). This suggests that most of these deaths occurred during young adulthood. We analysed our cohort's records to assess if there might be any risk factors in these families that could predict the risk of death. Other than delays in diagnosis and access to first-line treatment options, no other factors appeared to predict the risk of mortality. A multicentre study from Germany has also reported that mortality was significantly higher in undiagnosed patients (63 of the 70 deaths) than in diagnosed patients with HAE (7 of the 70 deaths). Bork *et al.* reported that the average lifespan may be reduced by approximately 31 years because of HAE.[10]

It must be observed that the mortality data in most studies have been observed from countries where first-line treatment options were not available. In the last 10 years, the majority of reported studies have been from China, Brazil, Iran, South Africa, Romania and India, where availability of and access to first-line treatment options are still a major challenge (Table 3).[5,11,13,16] It must also be observed that there are several countries in which first-line treatment options for HAE are still not available, but those countries have not yet reported mortality data in their patients with HAE. Most developed countries who do have available first-line treatment options for HAE, and who can follow guidelines and provide home management of an acute episode, have been able to significantly reduce their HAE-related mortality.[10,17]

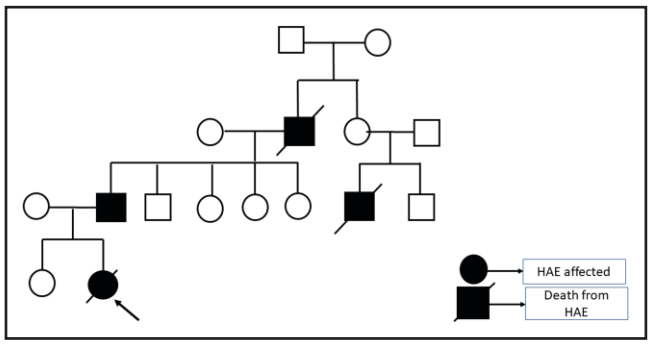

Figure 5 Pedigree of family 2. The index case succumbed to the laryngeal oedema while she was on long-term prophylaxis. HAE, hereditary angio-oedema.

At the time of analysis of these data, none of the first-line treatment options were available in India. Fresh frozen plasma (FFP) used to be the only treatment option available during an acute episode of angio-oedema[6]; however, FFP treatment has inherent limitations. First, it may not be as effective as many of the first-line treatment options such as plasma-derived C1Inh concentrate and icatibant.[4] Furthermore, delay in access is a likely challenge, as was seen in one of our patients, who could not access FFP during an episode of laryngeal oedema and died on the way to hospital. Additionally, FFP transfusions are not without adverse effects, which include: risk of transmission of viral infections (such as hepatitis B, human immunodeficiency virus and hepatitis C); allergic reactions; volume overload; transfusion-associated lung injury; and a theoretical risk of paradoxical flare of an acute attack.[18]

Nevertheless, studies from Iran and South Africa have reported that FFP may be effective in reducing mortality in patients with HAE.[19] Wentzel *et al.* reported that all but two patients in their series responded to the use of FFP.[19] In our published experience, whenever FFP was used during an acute attack, most patients showed a good response. However, it must be stressed that FFP should not be considered as a first-line treatment option for the management of acute attacks of laryngeal oedema in countries where plasma-derived C1Inh concentrate or other first-line treatment options are available.

There are several suggested ways to reduce the risk of death in patients with HAE and to improve the quality of life of these patients. For prompt diagnosis and appropriate management, education of the primary physicians treating HAE, especially in the emergency department,

Table 1 Comparison of clinical and molecular profiles between families who reported death from hereditary angio-oedema and those who reported no death

Characteristics	Families with mortality ($n=16$)	Families without mortality ($n=49$)	*P*-value
Type I : type II	13 : 3	45 : 4	0.35
Laryngeal oedema	14 (88)	36 (73)	0.32
Tongue swelling	6 (38)	25 (51)	0.34
Abdominal involvement	10 (63)	32 (65)	0.83
Extremity swelling	12 (75)	28 (57)	0.25
Genital swelling	8 (50)	24 (49)	0.94
Variants in *SERPING1* other than missense	5 (31)	16 (33)	0.58
Missense variants in *SERPING1*	6 (38)	15 (31)	0.61

Data are presented as *n* (%) unless otherwise indicated.

Table 2 Comparison of clinical manifestations between patients with hereditary angio-oedema who reported the death of at least one family member vs. patients who reported no deaths in their family

Characteristics	Patients who reported death of at least one family member ($n=56$)	Patients who reported no deaths in their family ($n=114$)	*P*-value
Age at onset, years; median (range)	11.5 (6–28)	14.5 (4–42)	0.71
Delay in diagnosis, years; median (range)	18 (1–40)	13.5 (2.5–32)	0.47
Laryngeal oedema	30 (54)	50 (43.9)	0.23
Tongue swelling	14 (25)	19 (16.7)	0.19
Abdominal involvement	34 (61)	60 (52.6)	0.12
Extremity swelling	50 (89)	91 (79.8)	0.14
Genital swelling	10 (18)	26 (22.8)	0.45

Data are presented as *n* (%) unless otherwise indicated.

Table 3 Review of published studies on mortality due to laryngeal oedema in large cohorts of patients with hereditary angio-oedema (HAE)

Author, year, country	Single-/ multi centre study	Total no. patients	Total no. deaths reported on follow-up	No. families reporting death of relative/s from HAE	No. family members who died of HAE	Age (years) at death, median (range)	Diagnosis of HAE before death	First-line treatments available
Bork, 2000,[12] Germany	Multi-	153	6 (3.9%)	15	23	39 (9–78)	3	No
Bygum, 2009,[21] Denmark	Nation-wide survey	82	None; deaths of 11 relatives reported in 5 families	5	11	NR	NR	No
Zilberberg, 2011,[22] USA	Multi-	145	9	NR	NR	NR	NR	NR
Lei, 2011,[23] Taiwan	Single	19	1	1	NR	NR	1	NR
Bork, 2012,[10] Germany	Multi-	728	70	56	NR	40.6 (9–78)	7	Yes
Kim, 2014,[17] USA	Multi-	NR	600 deaths in patients with HAE; 270 from laryngeal oedema	NR	NR	NR	NR	NR
Kargarsharif, 2015,[15] Iran	Multi-	51	2	5	3	28 (27–29)	2	NR
Coovadia, 2018,[14] South Africa	Multi-	43	2	NR	NR	NR	2	Yes
Moldovan, 2018,[16] Romania	Multi-	96	4	4	24	47 (11–59)	3	NR
Barbosa, 2019,[11] Brazil	Multi-	90	Nil	29% families	NR	NR	NR	NR
Cao, 2020,[13] China	Multi-	326	Not given	NR	30	46	NR	NR
Jindal, 2021,[5] India	Single	32	1	NR	3	NR	1	No
Present study, 2023, India	Single	170	1	16	35	38 (17–55)	1	No, at time of writing

NR, not reported.

is of paramount importance. Family screening should be emphasized in every family with newly diagnosed HAE so that the risk of death in undiagnosed cases can be lowered and deaths prevented.[20] Plasma-derived C1Inh concentrate should be made widely accessible to all patients with HAE. Efforts should be made to make available the other first-line treatment options for management of HAE such as icatibant (a bradykinin receptor antagonist) for an acute attack, and better treatment options for long-term prophylaxis such as lanadelumab (a plasma kallikrein inhibitor for subcutaneous use) and berotralstat (a plasma kallikrein inhibitor for oral use).

In conclusion, this is the largest single-centre cohort of patients with HAE in India reporting mortality data and factors associated with death in their respective families. Delay in diagnosis is the primary reason for mortality. It is extremely important to have access to first-line treatment options for HAE in India, especially for self-administration at home in an acute attack. There is an urgent need to increase awareness of HAE and to emphasize among families the importance of screening, in order to avoid and prevent delays in diagnosis.

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Conflicts of interest

All authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

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 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Departmental Review Board, Department of Pediatrics of the Postgraduate Institute of Medical Education and Research (ref. no. DRB-33-23, dated 04-05-2023). All patients gave written, informed consent for participation and publication of their case details.

References

1 Bork K. A decade of change: recent developments in pharmacotherapy of hereditary angioedema (HAE). *Clin Rev Allergy Immunol* 2016; **51**:183–92.
2 Maurer M, Magerl M, Betschel S *et al.* The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy* 2022; **77**:1961–90.
3 Minafra FG, Gonçalves TR, Alves TM, Pinto JA. The mortality from hereditary angioedema worldwide: a review of the real-world data literature. *Clin Rev Allergy Immunol* 2022; **62**:232–9.
4 Jindal AK, Reshef A, Longhurst H *et al.* Mitigating disparity in health-care resources between countries for management of hereditary angioedema. *Clin Rev Allergy Immunol* 2021; **61**:84–97.

5 Jindal AK, Rawat A, Kaur A *et al.* Novel SERPING1 gene mutations and clinical experience of type 1 hereditary angioedema from North India. *Pediatr Allergy Immunol* 2021; **32**:599–611.
6 Maurer M, Magerl M, Ansotegui I *et al.* The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy* 2018; **73**:1575–96.
7 Osler W. Landmark publication from The American Journal of the Medical Sciences: hereditary angio-neurotic oedema. 1888. *Am J Med Sci* 2010; **339**:175–8.
8 Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006; **119**:267–74.
9 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992; **71**:206–15.
10 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**:692–7.
11 Barbosa AA, de Oliveira Martins R, Martins R, Grumach AS. Assessment on hereditary angioedema burden of illness in Brazil: a patient perspective. *Allergy Asthma Proc* 2019; **40**:193–7.
12 Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000; **356**:213–17.
13 Cao Y, Liu S, Zhi Y. The natural course of hereditary angioedema in a Chinese cohort. *Orphanet J Rare Dis* 2020; **15**:257.
14 Coovadia KM, Chothia MY, Baker SG *et al.* Hereditary angio-oedema in the Western Cape Province, South Africa. *S Afr Med J* 2018; **108**:283–90.
15 Kargarsharif F, Mehranmehr N, Zahedi Fard S *et al.* Type I and type II hereditary angioedema: clinical and laboratory findings in Iranian patients. *Arch Iran Med* 2015; **18**:425–9.
16 Moldovan D, Bara N, Nădăşaan V *et al.* Consequences of misdiagnosed and mismanaged hereditary angioedema laryngeal attacks: an overview of cases from the Romanian registry. *Case Rep Emerg Med* 2018; **2018**:6363787.
17 Kim SJ, Brooks JC, Sheikh J *et al.* Angioedema deaths in the United States, 1979–2010. *Ann Allergy Asthma Immunol* 2014; **113**:630–4.
18 Kalaria S, Craig T. Assessment of hereditary angioedema treatment risks. *Allergy Asthma Proc* 2013; **34**:519–22.
19 Wentzel N, Panieri A, Ayazi M *et al.* Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. *World Allergy Organ J* 2019; **12**:100049.
20 Wong JCY, Chiang V, Lam K *et al.* Prospective study on the efficacy and impact of cascade screening and evaluation of hereditary angioedema (CaSE-HAE). *J Allergy Clin Immunol Pract* 2022; **10**:2896–903.e2.
21 Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol* 2009; **161**:1153–8.
22 Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in the United States 2004–2007. *Allergy Asthma Proc* 2011; **32**:248–54.
23 Lei W-T, Shyur S-D, Huang L-H. Type I hereditary angioedema in Taiwan – clinical, biological features and genetic study. *Asian Pac J Allergy Immunol* 2011; **29**:327–31.