Title: **Hereditary Angioedema type 1 experience in KwaZulu-Natal.**

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ABSTRACT

Introduction:
Hereditary angioedema type 1 (HAE1) is a rare autosomal dominant genetic disorder due to a mutation of the SERPIN 1 gene on chromosome 11 (11q12.1) that codes for the synthesis of the enzyme C1 esterase inhibitor (C1INH). HAE1 was first reported in KwaZulu-Natal among members of a Zulu family in Rural Northern KwaZulu Natal (the NM family) by E. Moran et al in 2008. We studied 4 consecutive generations of this family to determine the genetic burden, to identify the common clinical manifestations of HAE1 acute episodes, to review therapeutic challenges in this rural setting in comparison with world standards, and lastly to evaluate the socio-economic burden inflicted by the disease.

Methods:
29 NM family members with possible HAE1 were collectively identified by the family, and those unable to attend at least 1 of the 3 booked Medical Outpatients Department appointments were excluded, which resulted in a final study sample of 13. An interview was conducted and a family tree was drawn identifying affected individuals in 4 consecutive generations. Information concerning acute clinical presentations in the past year (2017) was documented. A questionnaire was used to obtain the relevant HAE1 associated socio-economic burdens. A chart review was done to identify the prophylactic and acute therapeutic strategies used by doctors in this region. Blood samples for C1INH levels, complement C3 and C4 were taken to make a diagnosis of HAE1, and C-Reactive protein (CRP) was taken to rule out an acute episode.

Results:
Polygamy as a local practice was found to be an important factor that perpetuated the genetic burden of the disease. When compared to the laboratories normal value indices, C1INH levels were significantly lower than that of the population mean (30 mg/dL), with a mean of 5.45 mg/dL (CI: 3.97 – 6.92, SD – 1.65, $p < 0.01$), and a variance of 2.71. C4 levels were also significantly lower than that of the population mean (0.25 g/L), with a mean of 0.03 g/L (CI: 0.0087 – 0.0513, SD – 0.0252, $p<0.01$), and a variance of 0.0006. The findings were suggestive of HAE1 in all participants individually.

Clinical features during acute attacks included angioedema of the extremities (100%), face (69%), neck (23%) and larynx (8%). Therapeutic strategies for acute attacks included Fresh Frozen Plasma (FFP) or Fresh Dried Plasma (FDP) depending upon availability of FFP. Danazol was the prophylactic drug of choice despite its potential deleterious side effects including virilization which occurred in one of the female participants. These treatment strategies were due to the unavailability of newer agents in this region. HAE1 has had a significant negative impact upon the socio-economic status of the NM family.

Conclusion:

HAE1 is a newly identified disorder in the broad spectrum of Allergy Medicine in KwaZulu-Natal. The diagnosis is simple to confirm, but requires a high index of suspicion. Therapeutic management still poses a challenge in this region due to lack of resources. Genetic counselling is of paramount importance bearing in mind the nature of the disease (autosomal dominant) and the local practice of polygamy. A support structure such as HAEi (Hereditary Angioedema International Organization) is highly recommended in raising awareness, improving therapeutic options via international liaisons and alleviating the socio-economic challenges posed by the disease.

MANUSCRIPT

Hereditary angioedema (HAE) is a disease characterized by recurrent episodes of angioedema without urticaria or pruritus that lasts for about 2 to 5 days, and is due to a non-histamine, bradykinin mediated allergic reaction associated with low levels of C1 esterase inhibitor (type 1), or normal levels but dysfunctional C1 esterase inhibitor (type 2), or normal levels and function of C1 esterase inhibitor (C1INH) with a mutation of factor XII of coagulation (type 3), or lastly with an unknown genetic or biochemical association (type 4) [1,2].

The South African context of HAE include 60 cases identified in the Western Cape Province, by KM Coovadia et al in 2017 over a period of 35 years. These were identified in Cape Town between the Groote Schuur Allergy Clinic and the Allergy Diagnostic and Clinical Research Unit at the University of Cape Town, Lung Institute [3]. In KwaZulu Natal, 10 years ago, 6 cases of HAE type 1 (HAE1) were identified by E. Moran et al at Hlabisa District Hospital, the so called NM family members [4]. This publication is geared towards sharing experiences around HAE1 in KwaZulu Natal, in view of increasing awareness among medical professionals, affected families and other interested stakeholders.

Objectives:

The initial cohort identified in KwaZulu Natal with clinical and serological manifestations of HAE1 only included 6 members of the NM family in 2008 (NM1, NM2, NM3, DM, SS, SM). We have studied the NM family further for the following reasons:

1. To review the current prevalence of HAE1 among members of the NM family.
2. To identify common clinical manifestations of HAE1 during attacks.
3. To compare therapeutic interventions with world standards.
4. To evaluate the socio-economic burden inflicted by HAE1 in this family.

Methods:

A total of 29 NM family members with possible HAE1 were collectively identified by the family members, and those unable to attend at least 1 of the 3 booked Medical Outpatients Department appointments were excluded since during these visits, consents were signed, blood tests taken, questionnaires distributed and individual interviews conducted. As a result, the final study sample comprised of 13 individuals.

Blood samples for C1INH levels, Complement C3 and C4, and C-Reactive Protein (CRP) were taken to confirm the diagnosis and exclude the possibility of an acute event at the time of obtaining samples. C4 can be lowered by an acute angioedema event; hence CRP samples were taken to exclude such a possibility [5].

Interviews were conducted and a family tree was drawn identifying affected individuals in 4 consecutive generations. Information concerning the acute clinical presentations during attacks in

the past year (2016 – 2017) was gathered. A chart review was conducted to identify the prophylactic and acute therapeutic strategies used by doctors in this region. And lastly, a questionnaire was designed to obtain the relevant information regarding HAE1 associated socio-economic burdens.

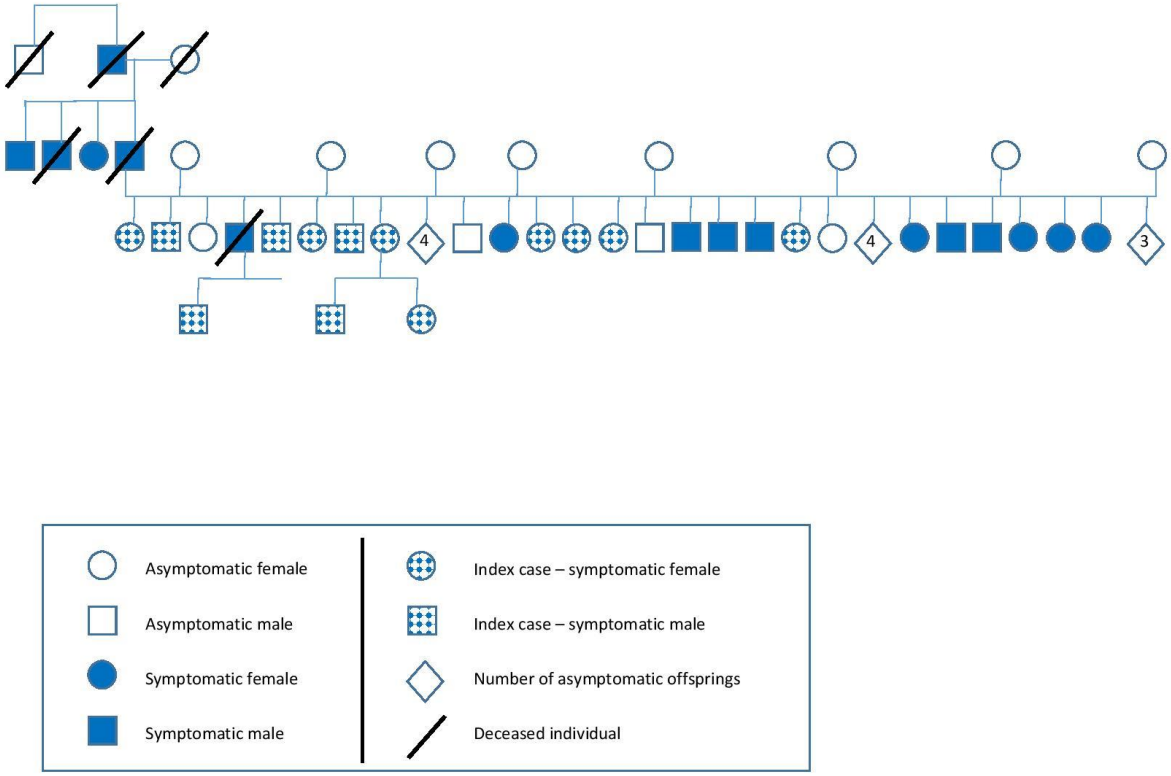
The questionnaire included the following:

1. How many times have you missed school / work due to an acute flare of HAE1 in the past 12 months? <3 times (1 point), 3-5 times (3 points), >5 times (5 points).
2. Have you repeated a grade at school or been suspended or demoted at work due to absenteeism at school / work secondary to hospital admissions or prolonged HAE1 related illness? YES (3 points), NO (0 points).
3. Have you ever been unable to participate in sports, trips, or any other social activity that has a potential to positively influence your future endeavors, but had to forfeit due to HAE1 related illness? YES (3 points), NO (0 points).
4. Have you ever been discriminated against taking up a position at school (prefect, etc.) or at work (promotion) due to your background of having HAE1? YES (3 points), NO (0 points).
5. Do you consider your current socio-economic status to have been negatively affected by your illness (HAE1)? YES (3 points), NO (0 points).

Results:

Out of 29 NM family members with clinical features suggestive of HAE1, 4 demised and 12 were lost to follow up. 13 family members were followed up in this study. Their demographics included ages ranging between 2 and 28 (mean age 12); 8 were females and 5 males (M:F ratio – 1:1.6); and all participants were black Africans in ethnicity. The partial genogram of the NM family (*see figure 1*) demonstrates a geometric increase in the prevalence of the disease. The factor seen to be responsible is the culture of polygamy.

FIGURE 1: Genealogy of the NM family



As per regional laboratory normal value indices (see table 1), C1INH levels of all the results received were significantly lower than that of the population mean (30 mg/dL), with a mean value of 5.45 mg/dL (CI: 3.97 – 6.92, SD – 1.65, $p < 0.01$), and a variance of 2.71 among family members. Similarly, C4 levels were also significantly lower than that of the population mean (0.25 g/L), with a mean value of 0.03 g/L (CI: 0.0087 – 0.0513, SD – 0.0252, $p<0.01$), and a variance of 0.0006 among family members. CRP levels were within the normal range.

A history of angioedema in association with decreased levels of C1INH, C4 and normal CRP levels is suggestive of the HAE1 diagnosis. C3 was normal except for one individual where it was borderline low. Usually C3 is normal in HAE since it is not affected by low levels of C1INH, as opposed to C4 [1,6].

The most common symptom during acute attacks was the swelling of extremities (100%), followed by facial swelling (69%), neck swelling (23%), and lastly laryngeal swelling (8%). There has been no historic report of abdominal and genital manifestations of acute HAE1 in this family.

Table 1. Clinical and laboratory screening data					
Patient, age, gender	**Clinical data** (2016 – 2017)	**C1INH** (21-39 mg/dL)	**C3** (0.90-1.80 g/L)	**C4** (0.10-0.40 g/L)	**CRP** (<10 mg/L)
DM1, 28 F	Face and extremities	7.4 L	1.23 N	0.03 L	<1
DM2, 7 M	Face and extremities	5.5 L	1.23 N	0.04 L	<1
DM3, 12 F	Neck and extremities	3.0 L	1.08 N	0.01 L	<1
DM4, 10 F	Face and extremities	5.6 L	1.10 N	0.07 L	<1
DM5, 14 F	Face and extremities	5.7 L	0.85 L	0.03 L	5
DM6, 8 F	Extremities	<2.8 L	1.44 N	0.00 L	Unavailable
DM7, 2 F	Face and extremities	5.0 L	0.82 L	0.03 L	<1
DM8, 6 M	Neck and extremities	Unavailable	1.17 N	0.01 L	<1
DM9, 9 F	Neck and extremities.	4.3 L	1.29 N	0.02 L	1
DM10, 11 M	Face and extremities	4.9 L	Unavailable	0.03 L	<1
DM11, 10 F	Face and extremities	7.8 L	1.32 N	0.01 L	2
DM12, 17 M	Face, Extremities and Larynx	7.8 L	1.26 N	0.02 L	5
DM13, 22 M	Face and extremities	5.6 L	1.04 N	0.09 L	6
ABBREVIATIONS: *C1INH* (C1 ESTERASE INHIBITOR). *CRP* (C-REACTIVE PROTEIN)					

Symptomatic NM family members are currently receiving Danazol as prophylactic therapy with all its potential deleterious side effects such as virilization, identified in one of the female participants and currently on Tranexamic acid (*see table 2*). Choosing this particular therapeutic agent is due to the unavailability and the cost of novel therapeutic options in South Africa at the moment. Acute attacks were mostly managed with Fresh Frozen Plasma (FFP) or Fresh Dried Plasma (FDP) depending on the availability of FFP which was the first choice.

Table 2. Acute and therapeutic strategies (2016 – 2017)	
Emergency therapy	FFP – 3 occasions FDP – 1 occasion (FFP was unavailable) Antihistamines & Steroids – 4 occasions cited above. Adrenaline – 0
Prophylactic therapy	Danazol – 10 participants Tranexamic acid – 1 participant (features of virilization while on Danazol) No therapy – 2

Out of the 13 participants, only 10 participated on the questionnaire since 3 participants were too young to comprehend some of the questions (*see table 3*). 5 questions were asked, and the answers were rated in a scale of 0 to 5 according to the severity of the response given. The results demonstrated on table 3 suggest that the socio-economic status of the participants has been affected moderately by the disease.

Table 3. Questionnaire results **Socio-economic burden secondary to HAE1** (10 participants / 5 identical questions each)	
QUESTIONS	ANSWERS ON AVERAGE
Question 1 (0-5 points)	3
Question 2 (0-3 points)	2
Question 3 (0-3 points)	1
Question 4 (0-3 points)	1
Question 5 (0-1 point)	1
TOTAL	8/15
Interpretation: Total of 15 points Category 1 (Mildly affected) : < 5 points Category 2 (Moderately affected) : 5 – 10 points Category 3 (Severely affected) : > 10 points	

Discussion:

HAE is a fairly new clinical entity in South Africa having been identified for the first time less than 40 years ago. HAE1 is secondary to a mutation of the SERPIN 1 gene on chromosome 11 (11q12.1) causing decreased levels of C1INH responsible for the inhibition of various proteases among which complement proteases such as C1r, C1s, MASP1 and MASP2 are included. The decreased levels of this protease inhibitor leads to a cascade of events that culminate with increased

bradykinin that results in angioedema, the herald feature of HAE with a potential to affect multiple organs [3,7].

The complete pathophysiology that leads to the release of bradykinin is still unclear, but heat shock protein 90, activated factor XII, and kallikrein are implicated among the initial steps. C1INH is responsible for the regulation of the levels of bradykinin among other functions such as the regulation of the complement classical pathway via the inhibition of C1 complex which cleaves C4. C1INH deficiency leads to a dysregulation of bradykinin production, with excess bradykinin causing the manifestations of angioedema by increasing vascular permeability, and the exaggerated C4 cleavage by C1 complex due to failure to inhibit the C1 complex [8, 9, 10].

The clinical presentation of an acute attack of HAE1 typically includes swelling of the face, tongue, larynx, neck, extremities, genitals and intra-abdominal organs. These clinical features are associated with a low C1INH, and a low complement C4. In making a diagnosis of HAE1, it is important to note that 25% of HAE1 is due to de novo mutations, and that normal C4 levels does not exclude the diagnosis in approximately 10 % of cases, hence a negative family history and a normal C4 level does not exclude the possibility of HAE1. Genetic testing is not necessary to establish the diagnosis of HAE1. It is also important to differentiate between hereditary and acquired angioedema since some modalities of the latter can be prevented by simply restricting exposure to the trigger factor such as the case of ACE inhibitors [1,6].

The success in the management of acute attacks is highly reliant upon early detection and early initiation of treatment, preferably at home [11]. First line therapies in the first world countries include a plasma-derived C1INH concentrate (Cinryze, Berinert) [12], Recombinant human C1 inhibitor (Conestat alfa, Rocunest)[13], Synthetic bradykinin beta 2 receptor antagonist (Icatibant) [14], and a Recombinant plasma kallikrein inhibitor (Ecallantide) [15] among other agents. The usage of Adrenalin, Corticosteroids and antihistamine is not effective during the acute attacks of HAE1. Fresh Frozen Plasma (FFP) is the alternative of choice in the absence of these novel therapeutic options [16].

Short or long-term prophylaxis should be given to all HAE1 patients since there is a more than 50% chance of developing acute laryngeal attack in all HAE1 patients at least once in their lifetime, and these episodes can be fatal. Attenuated androgen (Danazol) use to be the drug of choice for prophylaxis, but is neither cheap nor convenient due to long term side-effects such as virilization in females, and liver cancer. Tranexamic acid has also been used for long term prophylaxis [17,18]. Head to head studies are still to be done to evaluate and compare the efficacy of Danazol and Tranexamic acid [19]. The prophylactic agents used in Europe and America include kallikrein inhibitor [20], recombinant C1INH [21], among other agents.

European studies demonstrated HAE to have a significant socio-economic burden upon affected individuals and their immediate families in terms of direct medical costs and indirect costs related to lost productivity [22,23]. This socio-economic burden can only be expected to be exponential in a family that is situated in a rural area of a third world country like South Africa, already with a background of socio-economic challenges.

Conclusion:

HAE1 is a newly identified disorder in KwaZulu-Natal and falls within the broad spectrum of Allergy Medicine. The diagnosis is simple to confirm but requires a high index of suspicion. Therapeutic management still poses a challenge in this region mainly due to lack of resources. Genetic counselling is of paramount importance bearing in mind the nature of the disease (autosomal dominant) and the local practice of polygamy. A support structure such as HAEi (Hereditary Angioedema International Organization) is highly recommended in raising awareness, improving therapeutic options via international liaisons, and alleviating the socio-economic challenges posed by the disease in this region.

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