Case Report

HEREDITARY ANGIOEDEMA – HOW IS THIS MANAGED IN PREPARATION FOR PREGNANCY?

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INTRODUCTION AND CLASSIFICATION OF HEREDITARY IDIOPATHIC ANGIOEDEMA

Hereditary angioedema (HAE) is a rare disease that is inherited in an autosomal dominant fashion. The hallmark of the disease is the development of spontaneous and recurrent episodes of angioedema. Importantly, these episodes of angioedema occur in isolation, without urticaria or pruritis. The disease has no gender predominance. Left untreated, the mortality can be as high as 30 per cent.

In low- to middle-income countries (LMICs) such as South Africa, the treatment modalities include therapeutic fresh frozen plasma (FFP), anti-fibrinolytics and androgens. The more expensive and effective treatments available internationally are not readily available in South Africa. Danazol (an androgen) is teratogenic and cannot be used during the period of conception or during pregnancy.

We present a case of a young woman with HAE who desires to fall pregnant and have a baby of her own. In our discussion, the authors describe HAE and the pathogenesis of this condition. Treatment strategies are explored with specific reference to conception and pregnancy.

CASE PRESENTATION

Patient AZ is a young woman who lives in Johannesburg. She has inherited a terrible and strange disease from her mother. She develops spontaneous swellings of parts of her body in an asymmetric fashion that last 3–5 days before spontaneously resolving. During these episodes of swelling she often suffers from agonising abdominal pain. On two occasions, she developed life-threatening laryngeal oedema and almost required ventilation for upper-airway obstruction. In the past, she had previously witnessed her mother suffocate to death from the same disease. Figures 1 and 2 illustrate the angioedema attacks that patient AZ has endured previously.

The medical professionals from whom she sought help previously thought that she had severe allergies; however, no obvious trigger was identifiable. She was finally diagnosed with HAE after referral to an allergy unit in a tertiary centre. The diagnosis was confirmed with low levels of Complement 4 and low levels of C1 esterase inhibitor. She was finally diagnosed with HAE type 1, the most common type. After confirmation of the diagnosis, treatment with Danazol was initiated. Unfortunately, because of the risk of teratogenicity, she was advised against falling pregnant.

Figure 1: Angioedema of the face during a period of severe life-threatening laryngeal oedema

Figure 2: Asymmetric swelling of the hands during a period of cutaneous angioedema

Then she met her partner and wanted to marry. Her culture prohibits marriage if she cannot have children. She had a fervent desire to have a baby and live a normal life; but because of the teratogenicity of Danazol, this was not an option.

After many years of exploring different possibilities, her doctors finally received a breakthrough. After consulting with an international company that supplies C1-INH, patient AZ was given the opportunity to use the plasma-derived preparation during the period of conception and pregnancy. This occurred after approval was obtained from the South African Health Products Regulatory Authority (SAHPRA).

Patient AZ is trained in the self-administration of C1-INH. She has had six attacks in 12 months that required C1-INH administration. She eagerly awaits falling pregnant and having a baby of her own.

DISCUSSION

HAE is thought to occur at a prevalence of 1 : 50 000, with no gender or racial predilection.[1,2] Up to 40 per cent of patients will experience their first attack before five years of age, and up to 75 per cent by the age of 15. However, the diagnosis is made only by the second or third decade of life.[3]

Angioedema on its own can result from either a histamine or a bradykinin. Bradykinin-mediated angioedema can be either hereditary or acquired. The acquired forms are usually the result of the use of angiotensin-converting enzyme inhibitor (ACEi).[4]

There are a number of subtypes of HAE. The most common are types 1 and 2; with type 1 being the most common subtype, occurring in 85 per cent of patients.[3] Types 1 and 2 are inherited in an autosomal dominant pattern of inheritance; however, *de novo* mutations do occur in a small percentage of patients. Rare forms of the disorder exist due to mutations of the Factor X11 or plasminogen gene. The rare forms of the disease are associated with normal C4, normal C1-INH levels and function. This article concentrates specifically on types 1 and 2, the other subtypes being beyond the scope of this article. The distinguishing features from a laboratory perspective are illustrated in the table below:[3,4]

TABLE I: DISTINGUISHING FEATURES OF HAE-1 AND HAE-2

	C1-INH FUNCTION	C1-INH LEVELS	C4
HAE-1	Low	Low	Low
HAE-2	Low	Normal or high	Low

HAE generally affects three anatomical areas:[3]

1. *The skin (cutaneous attacks):* these are by far the most common. The oedema associated with this manifestation is non-pitting in nature. The affected sites are usually the face, the genitals and the extremities, although any site can be affected. The swelling is usually asymmetric and it is not associated with pruritis and urticaria. The swelling spontaneously resolves within 3–5 days.
2. *The gastrointestinal tract (GIT):* symptoms of abdominal pain, diarrhoea, abdominal bloatedness, nausea and vomiting all arise as a result of bowel-wall oedema. Gastrointestinal symptoms can occur in isolation and, in a minority of patients, this can be the only presenting feature.
3. *The upper airway (laryngeal attacks):* these attacks are by far the most concerning. Left untreated, they can result in fatal asphyxiation. Laryngeal swelling can occur either in isolation or in association with swelling of the lips, tongue, uvula and soft palate. Up to 50 per cent of patients with HAE will experience one episode of laryngeal oedema in their lifetime, and some may experience recurrent symptoms.

Identifiable triggers of attacks include:[3]

- minor trauma;
- oral and dental procedures preceding laryngeal attacks;
- medications including oestrogen-containing drugs such as the combined oral contraceptive, hormone-replacement therapy and tamoxifen;
- *H pylori* infections;
- hormonal changes, including puberty and pregnancy.

The diagnosis of HAE rests on a good history and examination and relevant laboratory confirmation. The diagnosis should be suspected when patients present with recurrent episodes of angioedema. The following support the diagnosis:[4,5]

- A positive family history – this may not be present in 25 per cent of cases.
- The occurrence of symptoms in childhood or adolescence.
- Recurrent painful abdominal symptoms.
- Failure to respond to the conventional methods of managing allergy or anaphylaxis, including glucocorticoids, antihistamines or adrenaline.
- An attack of laryngeal oedema.
- The absence of urticaria with symptoms.

Laboratory testing based on clinical suspicion involves C4 levels, C1-inhibitor (C1-INH) protein levels and C1-INH-function studies (see Table I above). C1-INH-function studies are not readily available in South Africa, especially in the public sector.

In December 2017, the World Allergy Organisation/*European Academy of Allergy and Clinical Immunology (WAO/*EAACI) published a position statement on the management of HAE.[4] Treatment should ensue in all patients in which a diagnosis is confirmed. Therapy can be based either on an 'on-demand' strategy or on 'long-term prophylaxis'. For an on-demand strategy, the following classes of drug can be used:

- *C1-INH concentrate:* this is available in two preparations – plasma-derived or recombinant. The two plasma-derived drugs approved for on-demand use are Berinert and Cynrize. Both of these are well tolerated and adverse events are minimal. Ruconest is the only recombinant human C1-INH available.
- *A kallikrein inhibitor:* the only obtainable kallikrein inhibitor is Ecallantide, which is available in the United States for use in patients above 12 years of age. Hypersensitivity is a risk and, because of this, this drug is not licensed for self-administration. It therefore has to be administered by a healthcare professional.[6]
- *Bradykinin-receptor antagonist:* Icatibant is available internationally for use in adults above 18 years of age. The risk of hypersensitivity is low as compared to Ecallantide and the drug is accordingly registered for on-demand self-use.[7]

Long-term prophylaxis should be considered in all patients exhibiting a high disease activity in order to reduce the number of attacks. Suggested strategies include:[4]

- *Twice-weekly C1-INH concentrate:* this is the preferred choice of treatment. However, this is expensive and not readily available in all countries, especially not in South Africa.
- *Androgens:* these are suggested when C1-INH is not available.
- *Anti-fibronyltics:* these are not readily suggested for long-term prophylaxis as their efficacy has not been adequately demonstrated.

In South Africa, the agents suggested for on-demand use are not easily available. They are imported after SAHPRA approval on a patient-to-patient basis. These drugs are exceptionally expensive; and funding for them is also challenging. Danazol is the only available option for long-term prophylaxis in South Africa. However, the use of the drug comes with side-effects that include virilisation and interaction with other drugs, especially statins. It is absolutely contra-indicated during pregnancy because of its potentially teratogenic effects.

As this is an autosomal dominant condition, patients should be referred to a genetic counsellor. Genetic counsellors are available in both the public and the private sectors in South Africa.

HAE DURING PREGNANCY AND LACTATION[4,8,9]

The hormonal, anatomical and physiological changes that accompany pregnancy may alter the course of the disease in HAE. Pregnancy itself can either mitigate or aggravate the disease, or have no effect at all. It is very rare that the first attacks of the disease happen during pregnancy.

Internationally, C1-INH concentrate is the suggested treatment. Ecallantide, however, is not suggested. There are case reports for the use of Icatibant in pregnancy. An on-demand strategy can be employed in patients with a low attack frequency. However, in patients who have a higher attack frequency, long-term prophylaxis with C1-INH concentrate may be needed. If nothing else is available, FFP can be used on demand during severe attacks.

Vaginal delivery is the preferred method of delivery. Avoiding surgery and/or intubation is essential to avoid exacerbation. If surgery is necessary, however, then pre-procedural C1-INH concentrate is necessary prior to anaesthesia.

As with all other patient groups, anti-fibrinolytics may be used, but their efficacy is not proven. Androgens cross the placenta. The side-effects include masculinisation of the female foetus, intra-uterine growth restriction and placental insufficiency. As a result, the use of androgens during pregnancy is contra-indicated.

In summary:

- During the conception phase, it is advised that all androgens be discontinued two months prior.
- During pregnancy, androgens are completely contra-indicated for the reasons mentioned above. The options available in South Africa include on-demand FFP; unless one is able to gain access to C1-INH concentrate.
- During breastfeeding, androgens have been shown to be excreted in breastmilk and they are therefore contra-indicated during lactation. Lactation should be discontinued prior to commencing androgens again. In contrast to androgens, anti-fibrinolytics are safe during breastfeeding and remain an option for those living in South Africa (although their efficacy in preventing attacks has not been proven).
- The newborn should be watched closely for the development of spontaneous swellings of the body and the paediatrician should be made aware of the mother's diagnosis.

CONCLUSION

HAE is in itself a rare disease. Its diagnosis is missed very often, owing largely to a lack of awareness of the disease. Patients are commonly misdiagnosed as having severe allergies.

The available therapies in South Africa favour a long-term prophylaxis strategy to prevent angioedema attacks. The most commonly used and most effective agent is Danazol, but it is unfortunately contra-indicated during conception, pregnancy and lactation. International guidelines suggest the use of C1-INH during pregnancy and breastfeeding; however, it is not easily available is South Africa. A special motivation and funding are necessary to support patients of childbearing age who wish to lead a normal life and have a family of their own.

Patients should be managed by a multidisciplinary team, including obstetricians, immunologists/allergists, paediatricians, geneticists and genetic counsellors.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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