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Life-threatening hereditary angio-oedema: Challenges of care in South Africa

The report and description by Coovadia *et al.*[1] in this issue of *SAMJ* of a large cohort of patients in the Western Cape Province of South Africa (SA) suffering from type 1 hereditary angio-oedema (HAE) not only documents for the first time a significant presence of this life-threatening condition on the African continent but highlights the challenges of diagnosis and management in the SA socioeconomic and healthcare context.

The diagnosis of HAE is often missed or delayed, as illustrated by diagnosis as late as the fourth decade for some patients in the reported cohort. Failed diagnosis is due to lack of awareness among doctors. The average prevalence of HAE is 1:50 000, so we estimate that >800 individuals in SA may suffer from HAE. However, we estimate that only ~100 of these are actively diagnosed. The good news is that complement C4 levels are an invaluable and easy screening test for type 1 HAE, although availability in more remote settings may vary. C4 is low in most cases of HAE, especially during an attack (sensitivity >90%). Clinicians should perform screening for all patients experiencing non-pruritic episodes of asymmetrical angioedema without urticaria, particularly if there is a family history of swellings and the patient is not on an angiotensin-converting enzyme (ACE) inhibitor. Recurrent episodes of angio-oedema in the absence of ACE inhibitors should also be reviewed by a specialist, ideally an allergist. A low antigenic C1-esterase level confirms the diagnosis of type 1 HAE and can be accessed in larger National Health Laboratory Service and private laboratories. Since HAE is a Mendelian dominant condition, immediate family members should also be tested. Confirmation of the more unusual type 2 and 3 variants of HAE, which require functional C1-esterase inhibitor assays or genetic testing, respectively, is very difficult. Functional testing is no longer available in SA, while genetic diagnosis of type 3 HAE can only be accessed through certain private laboratories.

Patients with HAE should not die from acute attacks. This is the case in most developed countries with good healthcare access and registered effective treatments such as purified C1-inhibitor concentrate or bradykinin-β2-receptor antagonists. Unfortunately, it is not the situation in SA and most other developing-country settings. In our cohort we report two deaths; both were public sector patients with poor access to health facilities, no transport and no available effective medicine to keep at home on standby for attacks.[1] In addition, we were recently saddened by two further HAE deaths that illustrate the role of patient education and circumstance in affecting the outcome of HAE. The first casualty, a known patient's sister, had refused testing and prophylactic management and died of her first laryngeal attack, out of hospital. The second also died out of hospital, but after repeated admissions for acute attacks, including an admission direct from police custody following arrest for drug dealing; he was a member of a local gang and never adherent to our prescribed prophylaxis.

In SA and other developing countries, management of the acute attack is a therapeutic dilemma. Importantly, steroids and antihistamines are completely ineffective for the treatment of acute attacks of angio-oedema in HAE patients, as the oedema is bradykinin-mediated. Intravenous purified C1-inhibitor concentrate, available for many years overseas as Berinert, is first-line treatment in most countries, and is extremely effective in rapidly reducing the oedema. We have imported it on a named-patient basis for several of our patients and have used it both for acute severe attacks and prophylactically for patients undergoing major surgical procedures (e.g. hip replacement). C1-inhibitor concentrate is also safe for use in children. A new highly effective subcutaneous treatment for life-threatening attacks, but not for prophylaxis, is icatibant, the bradykinin receptor antagonist. Icatibant is not registered in SA, although patients in our reported cohort were fortunate to participate in the first global multicentre phase 3 clinical trials;[2] a few continue to access and self-administer this life-saving therapy at home through post-trial access. The response to these two targeted therapies is rapid, potentially allowing hospital discharge in a few hours on the same day, saving the time and cost of intensive care unit or high-care admission. We cannot access either of these targeted therapies for the majority of our public sector patients with acute attacks. Fresh frozen plasma (FFP) has been used in under-resourced areas for life-threatening attacks, as fresh plasma contains some active C1-esterase inhibitor. There has, however, been very little documentation of its effectiveness in blinded or placebo studies,[3,4] although it is widely used empirically. Our experience, referred to by Coovadia *et al.*[1] suggests that FFP may indeed be helpful, but further studies looking at appropriate doses, timing of administration and treatment outcomes are necessary. FFP may result in anaphylactoid reactions, and like any plasma product carries an infectious transmission risk. Ideally all emergency rooms would have one of these therapies available. However, as highlighted in our reported deaths, even FFP availability is restricted to major centres and may simply be too far away and difficult to access. Home-based targeted therapy would be optimal, but cost and registration are prohibitive. For our patients, effective prophylaxis is imperative.

Berinert and other longer-acting C1-inhibitor concentrates, as well as novel kallikrein inhibitors, are available in many countries as prophylaxis. We are limited to the use of 17α-alkylated androgens such as danazol and the antifibrinolytics such as tranexamic acid. Our reported cohort outcomes show danazol to be both well tolerated and effective, and in the absence of more modern and safer prophylactic agents in SA it remains first-line treatment. It can even be used in younger children on a per kilogram adjusted dosage, especially when antifibrinolytics such as tranexamic acid are ineffective. Different patients respond variably to danazol and some develop side-effects, so that the lowest effective dose needs to be determined for each patient and careful monitoring for androgenic side-effects is an ongoing concern. Danazol is contraindicated during pregnancy, and we have successfully motivated for Berinert therapy in these special circumstances.

We hope that with the improved awareness associated with the publication of this SA cohort, more doctors will realise the significance of this disease in SA, think to investigate, and refer for treatment. In addition, we hope that state and private sector funders understand the challenges of life-saving treatment and access to services. We continue to support patient and allergy

advocacy groups that support and give a voice to these vulnerable patients.

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