Brief Report: A Solemn Reminder of the Mortality Risk Associated With HAE

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INTRODUCTION

Hereditary angioedema (HAE), caused by congenital C1 esterase inhibitor (C1-INH) deficiency, has long been recognized as a life-threatening condition. One of the earliest accounts of this condition describes asphyxiation in affected families. Individuals with HAE continue to be described as “critically ill,” a description logically generated by the natural history of HAE attacks in the absence of effective therapy. Over the past 3 decades, tremendous advances have been made in the management of HAE, including the clinical development of C1-INH replacement products (Cinryze®, ViroPharma Inc; and Berinert®, CSL Behring); a kallikrein inhibitor, ecallantide (Kalbitor®; Dyax Corp); and a bradykinin receptor antagonist, icatibant (Firazyr®, Shire Human Genetic Therapies, Inc). These novel therapies have only become available more recently in the United States, while other parts of the world, particularly Europe, have had a longer experience with such HAE therapies. Unfortunately, some countries still have restricted or nonexistent access to any HAE therapy.

Acute HAE attacks, especially those involving laryngeal edema, can be fatal. About 50% of patients with HAE will experience laryngeal edema at some point in their life. A subset of these patients experience recurrent episodes of laryngeal edema. Case reports of asphyxiation in the setting of laryngeal attacks in patients with HAE have been reported in both children and adults. The danger and potentially fatal nature of HAE attacks. Time of onset of an acute laryngeal attack has been reported to be as short as 20 minutes in one child. Another recently published study described 3 phases of fatal laryngeal attacks: phase 1 starting at the first recognized symptoms, which include feeling of a lump or tightness in the throat and difficulty swallowing; phase 2 at the start of dyspnea; and phase 3 at loss of consciousness. The mean duration of phase 1 was 3.7 hours, phase 2 was 41 minutes, and phase 3 was 8.9 minutes. Not all patients experienced phase 1; 6 of the 36 investigated patient deaths did not report phase 1.

Evidence of continued mortality from laryngeal edema even in diagnosed patients confirms the swift and potentially fatal nature of HAE attacks.

The benefits of the novel HAE treatments are clear—HAE attacks can now be terminated quickly and effectively, assuming the symptoms are recognized and timely access to treatment is secured. In the United States, there is a sense that we can now move from a historic goal of preventing mortality due to HAE toward the goal of achieving a more “normal” quality of life for all patients with HAE. Sadly, we have been reminded lately that substantial mortality remains attributable to this disease.

In the past 4 years, even with novel US Food and Drug Administration–approved HAE therapies, the US HAEA, a patient advocacy organization, has documented 7 deaths that are directly attributable to acute HAE attacks. These 7 patients ranged in age from 25 to 59 years, with a mean age of 38 years. An additional 3 HAE patient deaths were reported during that time period to have been possibly related to adverse effects from older HAE therapies. These included one opioid overdose in a young woman and fatal myocardial infarctions in 2 men only 39 and 45 years old. While the role of older HAE treatments, like chronic androgen therapy, in causing premature coronary events has not been established, it is concerning to see such events in relatively young individuals. The
detrimental effects of androgens on lipid profiles must be considered. These deaths likely underrepresent HAE-related mortality, as they include only those disclosed to a patient organization. However, such data highlight the need for continued awareness of this potentially fatal disease and clearly demonstrate that the ability of physicians to prescribe highly effective medications alone does not neutralize the danger of this condition.

Before the introduction of attenuated androgens as a preventive therapeutic agent in HAE, the mortality in some HAE patient family cohorts was reported to be as high as 25% to 50%. Prophylactic androgen therapy represented an important step toward mortality prevention by reducing the number of attacks experienced by patients with HAE. However, attenuated androgens are associated with significant adverse effects, including weight gain, virilization, increase in liver enzymes, alterations in lipid profile, and arterial hypertension, in addition to an increased risk of hepatocellular carcinoma with chronic use. Antifibrinolytics therapies such as epsilon-aminocaproic acid or tranexamic acid, used successfully for the prophylactic treatment of select patients with HAE, also carry significant adverse effects including diarrhea, postural hypertension, fatigue, increased muscle enzymes, and thrombosis. The emergence of therapeutic options such as the C1-INH replacement products, icatibant, and ecallantide has improved the management of HAE and can terminate angioedema attacks, with potentially fewer adverse effects compared to older therapies. Because of the mortality associated with this disease, there remains a strong need for therapeutic interventions to prevent fatal angioedema attacks in these patients.

One recurring theme among patient reports to the US HAEA is the gravity of the burden of illness HAE places on affected individuals and their family members. Not only does HAE carry significant morbidity and mortality for those affected, but the condition is associated with considerable psychological and financial costs. The psychological impact of a familial, potentially fatal condition is difficult to quantify, though quality-of-life measures using health surveys in a defined HAE population suggest that these patients are much more likely to receive psychotropic medications compared with the general population. Direct medical cost, especially emergency department visits and hospital stays, are quite substantial for these patients. Furthermore, patients affected by the unpredictable nature of HAE attacks lose a significant number of work days, posing an additional financial and emotional stressor. Although data on the psychological, social, and financial impact of HAE have been limited, a larger-scale European study, the Hereditary Angioedema Burden of Illness Study, is currently under way and will further illuminate the economic and humanistic impact of this disease on patients.

Since the first description of HAE by William Osler in 1888, tremendous strides in the management of this hereditary disease have been made. Despite these advances, patients with HAE continue to have increased rates of early mortality, demonstrating the need for continued, concerted efforts to increase disease awareness, to improve accurate diagnosis, and to implement effective management plans. Ideally, progress in these areas will introduce an era in which HAE deaths are reported only in historical descriptions of the condition.

REFERENCES


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