

[EDITORIAL]

Hereditary Angioedema from 1888 to 2018 -Progress and Problems

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Hereditary angioedema is an inherited disease characterized by recurrent episodes of non-pruritic edema of the skin and the submucosal tissues that are associated with abdominal pain attacks and life-threatening airway swelling (1, 2). This disease entity was first described clinically and genetically by William Osler in 1888 who originally named it “hereditary angioneurotic edema (HANE)” (3). It took 75 years from Osler’s report until Donaldson and Evans identified the central role of C1 inhibitor (C1-INH) in the pathophysiology of HANE (4). Since their landmark breakthrough, significant progress has been made in research on this inherited disease. One of the most important points is that the name of the disease was changed to hereditary angioedema (HAE) by deleting the word, “neurotic”, when the contribution of “neurotic” or nervous factors was recognized as too little to cause edema. As of mid-2018, more than 450 different mutations have been reported in the region of C1-INH gene (*SERPING1*), based on the Human Gene Mutation Database. It is now known that deficiency of C1-INH leads to the activation of the contact (kallikrein-kinin) system, which eventually culminates in the overproduction of bradykinin. By binding to bradykinin B2 receptor (BKB2), bradykinin increases vascular permeability, vasodilation and contraction of nonvascular smooth muscle and acts as a main mediator of the pathophysiology of HAE. Clarifying the link between the complement system, including C1-INH, and the bradykinin-forming contact system has contributed to the development of a variety of treatment modalities for HAE (1). C1-INH (pdh C1-INH) is a disease-specific plasma-derived human drug that was first introduced in the 1970s in Europe and later approved in many other countries, including Japan. Other drugs include ecallantide, an inhibitor of kallikrein in the contact system, which was approved in 2009 in the US; and the BKB2 inhibitor icatibant, which was approved in 2008 in Europe and 2011 in the US. Nei-

ther of these new treatment modalities have yet been approved in Japan, making pdh C1-INH (Berinert P[®]) the only drug for HAE as of July 2018 (5).

In this issue of *Internal Medicine*, Honda et al. reported a patient with HAE who developed suffocation due to laryngeal edema and entered a life-threatening condition while he was away from home on business (6). The important point of this case is the delayed treatment with pdh C1-INH, which worsened his HAE attack. There are two reasons for this delay. First, home therapy by self-administration of Berinert P[®] is not approved in Japan. Japanese patients with HAE must visit clinics or hospitals to receive pdh C1-INH from medical staff. This process takes much more time than self-administration at home. Second, relatively few medical facilities have stocks of pdh C1-INH; Berinert P[®] is quite expensive, costing ¥99,202 per vial, with 2 vials usually needed to treat an attack (5). Furthermore, HAE is a rare disease, afflicting only an estimated 2,500 patients in Japan. The frequency of attack differs among patients and can even change throughout a patient’s lifetime. Patients therefore tend not to visit medical facilities to receive pdh C1-INH with regularity. These circumstances mean that keeping stocks of pdh C1-INH can be an economic burden on medical facilities. If HAE patients have acute attack, especially while away from home, as in the case reported by Honda et al., it can be difficult to locate a site to receive pdh C1-INH urgently. In order to improve the accessibility of pdh C1-INH, efforts are being made by a number of medical associations, such as the Japanese Association for Complement Research and the Japanese Dermatological Association, along with the patient associations for HAE and pharmaceutical companies.

Finally, I would like to briefly mention the most recent progress in the field of HAE. In 2000, a new type of HAE with “normal” C1-INH was reported in Caucasians (7, 8). A

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number of abnormalities in the genes for Factor XII, angiotensin-converting enzyme, and plasminogen have been identified in this novel disease entity in Caucasians (9-11). Recently, we identified a plasminogen gene mutation in HAE patients in Japan, the first report from an ethnic group other than Caucasians to identify a genetic basis for HAE with normal C1-INH (12). The establishment of treatment modalities of HAE with normal C1-INH is also awaited.

Author's disclosure of potential Conflicts of Interest (COI).

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