The *ABC* of Angioedema: Ace Inhibitor, *Bradykinin*, and *C1-inhibitor* Are Critical Players

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Angioedema is a sudden and self-limiting swelling affecting the skin, mucosa and visceral organs, such as the intestine and larynx. This condition is due to increased capillary permeability induced by drugs, food, infection, emotional stress, and sometimes an unknown etiology. Angioedema is mainly classified into three conditions: idiopathic, extrinsic factor-induced and C1-inhibitor (C1-INH) deficient (1, 2). In this issue of Internal Medicine, Nicolas et al. reported a comparison of the clinical manifestations of angiotensin-converting enzyme inhibitors (ACE-I)-induced angioedema and hereditary angioedema (HAE) (3). The former is included in extrinsic factor-induced angioedema and the latter in angioedema due to C1-INH deficiency.

ACE-I is one of the most important drugs for the treatment of hypertension as well as congestive heart failure and chronic kidney diseases. ACE-I competitively inhibits ACE and thus blocks the formation of angiotensin II from angiotensin I (4). Additionally, ACE degrades bradykinin and acts as an inhibitor of bradykinin. Therefore, ACE-I can induce increased levels of bradykinin, which culminates in increased capillary leakage and angioedema, although the mechanism is not fully understood. A congenital defect in carboxypeptidase N, which inactivates C3a, C4a, C5a, bradykinin, kalladin, and fibrinopeptides, is associated with recurrent attacks of angioedema (5). These findings support the notion that an increased bradykinin concentration due to its degradation defect may cause angioedema. The incidence of ACE-I-induced angioedema was shown to be 0.3% in a meta-analysis of 26 randomized trials (6). Because ACE-I is widely used in clinical practice, the number of angioedema-affected patients should be large enough to be investigated. Most of the patients taking ACE-I do not develop angioedema, thus suggesting there may be additional mechanisms or factors for the development of angioedema. In Japan, a nationwide survey in 2009 revealed the prevalence of ACE-I-induced angioedema to be 8% of all angioedema patients.

In that report, the prevalence of HAE was 12%, while that of idiopathic angioedema was 46%, which was higher than any other causes (7).

HAE is an autosomal dominant disease caused by mutations in the *C1-INH* gene. The defective *C1-INH* gene leads to either decreased levels of both C1-INH activity and protein (type 1) or decreased C1-INH activity with a normal to elevated protein level (type 2). C1-INH can inactivate serine proteases of the complement components C1r and C1s (complement cascade), kallikrein (contact cascade), plasmin (fibrinolytic cascade), and coagulation factor XII (coagulation cascade). Therefore, these 4 cascades are dysregulated in HAE. Elevated levels of bradykinin due to activated kallikrein and factor XII are considered to increase the vascular permeability in HAE (8). In contrast to ACE-I-induced angioedema where most of laboratory tests are normal, including complement, HAE can be diagnosed by the decreased levels of complement C4 and C1-INH activity (9). The guidelines for HAE diagnosis and treatment in Japan are noted in reference 10 (10).

Both ACE-I-induced angioedema and HAE are considered to stem from a common pathogenesis: an elevated bradykinin level and the resultant increased capillary permeability. Nicolas et al. (3) observed that swelling of the tongue, lips and larynx was significantly more prevalent in ACE-I-induced angioedema than HAE in their cohort. Conversely, abdominal attacks were significantly less frequent in their ACE-I-induced patients, which was in line with the previous observations (11). It is not clear why the clinical manifestations of ACE-I-induced angioedema and HAE are not same, although both are categorized as bradykinin-mediated diseases. However, there are two differences in the action mechanisms of ACE and C1-INH. First, ACE is involved in the degradation of bradykinin, while C1-INH is involved in the production of bradykinin. Second, both enzymes are multi-functional and target many unique substrates. These

factors may also be organ specific. It is possible that C1-INH plays a more important role for the inhibition of edema than ACE in the intestine. We should keep in mind that corticosteroids and anti-histamines are ineffective for both ACE-I-induced angioedema and HAE. In Japan, plasma-derived C1-INH concentrates are the choice therapy for HAE treatment. No treatment modality, other than the discontinuation of ACE-I, is currently available for ACE-I-induced angioedema, however, it is encouraging that icatibant, a bradykinin receptor antagonist, was shown to be effective for ACE-I-induced angioedema in a recent clinical randomized trial (12).

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