Contact System Activation and Bradykinin Generation in Patients With Idiopathic Angioedema

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Based on the underlying pathogenic mechanism, angioedema can be classified into 3 major categories: (*1*) histaminergic angioedema, which responds to antihistamine therapy; (*2*) bradykinin-mediated angioedema, which can be hereditary, angiotensin-converting enzyme inhibitor (ACEI)–related, and acquired C1-inhibitor (C1-INH) deficiency angioedema; (*3*) idiopathic angioedema, the causes of which are still unknown [1,2]. Some forms of idiopathic angioedema respond to antihistamines (idiopathic histaminergic angioedema), whereas others do not (idiopathic nonhistaminergic angioedema) [1]. Since the pathogenesis of increased vascular permeability remains unknown in about 10% of angioedema cases [3] and patients do not respond to antihistamines, the study of an alternative mediator such as bradykinin may open new diagnostic and therapeutic perspectives. A role for bradykinin has also been demonstrated in the pathophysiology of anaphylaxis and chronic urticaria [4,5], conditions in which mast cell involvement is considered predominant. Mast-cell activation may also be important in angioedema not responding to antihistamines, and several cases of idiopathic nonhistaminergic angioedema respond to anti-IgE treatment with omalizumab [6]. Bradykinin is a potent vasoactive peptide that is released from high-molecular-weight kininogen (HK) by plasma kallikrein during activation of the contact system. The cleavage of HK occurs at several points, enabling the release of bradykinin and resulting in breakdown products (cleaved HK) [7]. To date, the evaluation of contact system activation and bradykinin generation in vivo has been subject to methodological difficulties, with the result that reliable data are not always available [8]. However, the main problems, such as in vitro generation and degradation of bradykinin, can be solved using meticulous blood sample collection [9-11]. The aim of the present study was to evaluate

contact system activation and bradykinin generation during maximum disease activity, ie, at the exact moment the patient arrived in the emergency department.

We studied 9 patients during angioedema attacks (4 men and 5 women; age range, 32-83 years). The patients had no family history of angioedema, no known allergy, no C1-inhibitor deficiency, and no therapy with ACEIs or nonsteroidal anti-inflammatory drugs. All 9 patients had experienced episodes of angioedema not responding to antihistamines. A trained researcher collected blood samples in the emergency department. Nine healthy individuals, who were sex- and age-matched with patients, served as controls. The study was approved by the Ethics Committee Valpadana of ASST Ospedale Maggiore Crema (No. 104, March 22, 2019). We measured plasma levels of cleaved HK using SDS-PAGE/immunoblotting and of bradykinin using enzyme immunoassay. Angioedema-related genes were also analyzed [12]. Details on patients, methods, and the statistical analysis are shown in the supplementary material.

All patients had acute angioedema. This involved the face in 5 patients, lips in 3 patients, and both abdominal wall and feet in 1 patient. The demographic, clinical, and laboratory characteristics of patients are reported in Supplementary Table 1. Cleaved HK levels (Figure) were significantly higher in the angioedema patients (median 27.1%, range 22%-61.3%) than in the controls (20.5%, 9.5%-23.4%) (*P*=.0001). Bradykinin levels (Figure) were higher in the angioedema patients (8.21 ng/mL, 7.05-21.79 ng/mL) than in the controls (2.83 ng/mL, 1.96-3.99 ng/mL) (*P*=.0001). Bradykinin levels were directly correlated with levels of cleaved HK (r=0.893, *P*=.0001). No mutations were found in the genes implicated in the pathogenesis of hereditary angioedema (*SERPING1, ANGPT1, PLG, MYOF, KNG1,* and *F12*). All patients were treated with systemic corticosteroids (methylprednisolone 80 mg IV) and antihistamines (chlorphenamine 10 mg IV) and, based on oral or tongue involvement, also with epinephrine (1 mg IM) (Supplementary Table 2). Time to symptom resolution (ie, the median time corresponding to the complete disappearance of angioedema reported by the patient after discharge) was 30 hours (range, 15-48 hours) and was directly correlated with bradykinin levels (r=0.819; *P*=.007).

Our study shows that patients with idiopathic nonhistaminergic angioedema may generate higher amounts of the vasoactive peptide bradykinin owing to contact system activation. Indeed, we found that high plasma levels of bradykinin correlated directly with the levels of a marker of contact system activation, ie, cleaved HK. The pathophysiological involvement of bradykinin in the patients we report is also indicated by the direct correlation between plasma levels of bradykinin and the time to resolution of angioedema. The absence of angioedema-related genetic mutations we observed indicates that the disease is acquired. To our knowledge, this is the first demonstration that bradykinin can be generated through contact system activation in idiopathic angioedema; indeed, we simultaneously measured

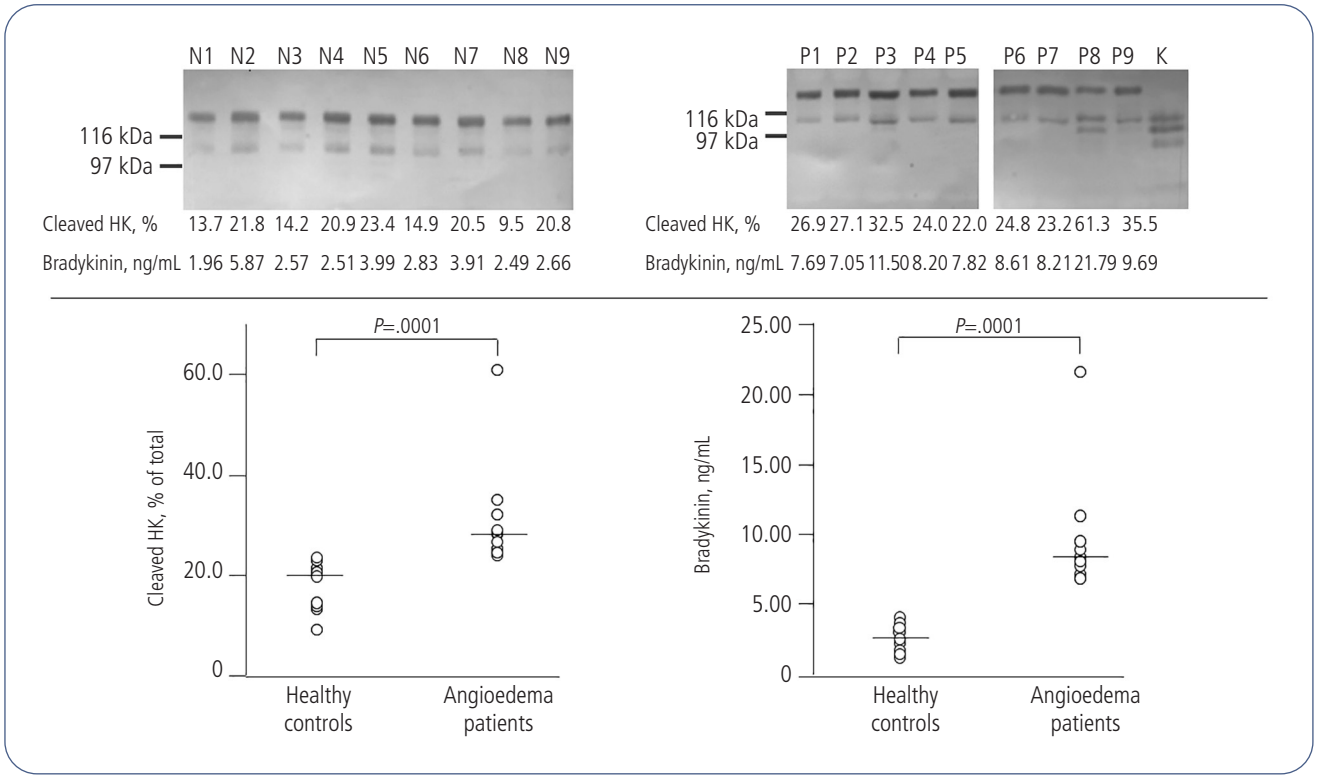

Figure. Upper panel. Immunoblotting of cleaved high-molecular-weight kininogen (HK) in plasma collected from healthy controls (N, left) and from patients (P, right). K indicates normal plasma treated with kaolin.
Lower panel. Cleaved high-molecular-weight kininogen (HK) (left) and bradykinin (right) plasma levels in angioedema patients and in healthy controls.

both levels of bradykinin and those of the marker of its generation through contact system activation (cleaved HK). Therefore, in nonhistaminergic idiopathic angioedema, the increase in bradykinin levels, which we observed here and in a previous report [13], is due to the activation of the contact system, as in angioedema due to C1-INH deficiency [9-11]. However, in angioedema due to C1-INH deficiency, previous data indicate that the contact system is activated 2 to 5 times more frequently during attacks [9-11]. Levels of bradykinin are also high in patients with acute angioedema due to ACE inhibitors [9,14], although their cleaved HK is normal [14]. Thus, in ACEI-associated angioedema, the increase in bradykinin is not due to increased generation of bradykinin, but rather to its reduced catabolism, which is normally sustained by ACE and, in this case, inhibited by therapy.

The limitations of our study were the small number of participants (due to the low incidence of the condition) and the lack of plasma samples from patients during remission. However, the sample size enabled a good power (80% with an α error of 5%), and blood samples could be taken in the emergency department, enabling us to obtain reliable measurements for the contact system and bradykinin at the peak of the acute angioedema attack.

In conclusion, our data indicate that the contact/kinin system is involved in the pathophysiology of some cases of idiopathic angioedema and may influence the duration of symptoms. If confirmed by larger studies, they may open new perspectives in this condition for evaluation of drugs that inhibit the contact/kinin system, as previously reported [15].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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