

RESEARCH LETTER

Bradykinin in idiopathic non-histaminergic angioedema

M. Cugno¹, A. Tedeschi² and J. Nussberger³¹Internal Medicine, IRCCS Maggiore Hospital, University of Milan, ²Internal Medicine, Fatebenefratelli Hospital, Milan, Italy and ³Internal Medicine, University Hospital, Lausanne, Switzerland

To the Editor:

Angioedema is a localized swelling of the subcutaneous and submucosal tissues that is frequently associated with urticaria but that can also occur alone. It can become life-threatening when the larynx is involved or painful when the gastrointestinal tract is affected. Angioedema without weals can be hereditary or acquired. Four acquired angioedema types have been identified: one associated with C1-inhibitor deficiency, one due to treatment with angiotensin converting enzyme (ACE)-inhibitors and two types with no identified cause (one responding and one not responding to H1 antihistamines) [1]. The increase in vascular permeability underlying the appearance of angioedema is due to the release of vasoactive mediators, namely histamine and bradykinin. Increased plasma levels of bradykinin have been demonstrated in patients with acute attacks of angioedema due to C1-inhibitor deficiency or ACE-inhibitor therapy, and normal bradykinin levels have been found in patients with histaminergic angioedema [2, 3]; on the contrary, to date, a clear demonstration of bradykinin involvement in idiopathic non-histaminergic angioedema is lacking.

This may be due in part to the extreme difficulty to measure bradykinin in human plasma owing to its very low concentration (pM), its short half-life (seconds), its quick enzymatic generation and degradation during sampling and handling procedures and interference by precursor molecules, catabolic products and other kinin peptides. The only possibility to obtain reliable data in plasma bradykinin measurement is to perform a laborious procedure characterized by the block of protease and peptidase activity during sampling procedures, liquid-phase extraction in order to eliminate proteins, high-performance liquid chromatography to eliminate precursor molecules and catabolic peptides of bradykinin and finally detection by a high-sensitivity radioimmunoassay [2].

We measured plasma bradykinin levels in four patients with idiopathic non-histaminergic angioedema observed in six different attacks, one also during remission and three patients with acute attacks of

ACE-inhibitor-related angioedema. Twenty healthy subjects served as normal controls. Figure 1 shows increased levels of bradykinin in all the attacks of idiopathic non-histaminergic angioedema [median 46.5 fmol/mL (min 13 fmol/mL–max 60 fmol/mL)] and of ACE-inhibitor-related angioedema [median 30 fmol/mL (min 14 fmol/mL–max 45 fmol/mL)]. On the contrary, the patient observed during remission had normal levels (6.3 fmol/mL) (normal range: 0.2–7.1 fmol/mL). Control plasma samples from 20 healthy subjects showed median bradykinin levels of 3.7 fmol/mL (min 0.9 fmol/mL–max 6.4 fmol/mL). On comparison, patients with hereditary angioedema due to C1-inhibitor deficiency (type I) and C1-inhibitor dysfunction (type II) showed levels of 16–90 fmol/mL during acute attacks and 3–12 fmol/mL during remission [2]. A difference in bradykinin plasma levels between acute attacks and remission was also observed in patients with ACE-inhibitor-related angioedema: 45–47 fmol/mL during attacks vs. 3.2–6.6 fmol/mL during remission [2, 4]. Normal subjects assuming ACE-inhibitors showed only a slight increase in plasma kinins following ACE-inhibitor administration [5]. On the contrary, bradykinin measurement showed a marked increase during acute attacks of angioedema and normal levels during remission.

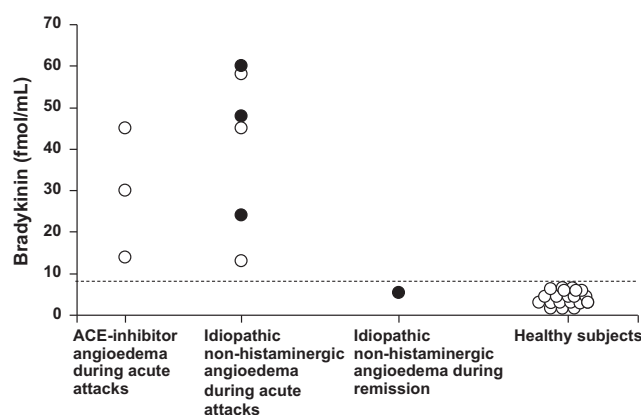


Fig. 1. Plasma bradykinin levels in three patients with angiotensin converting enzyme (ACE)-inhibitor-related angioedema and in four patients with idiopathic non-histaminergic angioedema observed in six different attacks and once during remission (the filled symbols represent three different attacks and one remission). Twenty healthy subjects served as controls. Dotted line represents the upper limit of the normal range.

Correspondence:

Massimo Cugno, Internal Medicine, Department of Pathophysiology and Transplantation, University of Milan, Via Pace 9, 20122 Milano, Italy.
E-mail: massimo.cugno@unimi.it

Our data confirm the involvement of bradykinin in ACE-inhibitor-induced angioedema and demonstrate bradykinin formation during attacks of idiopathic non-histaminergic angioedema, thus providing the rationale for the clinical use of bradykinin antagonists in both conditions. A recent clinical trial on icatibant use in ACE-inhibitor-induced angioedema [6] and some anecdotal reports in idiopathic non-histaminergic

angioedema [7, 8] further support the pathogenetic role of bradykinin in these conditions.

Funding

Research grant from Ricerca Corrente, IRCCS Maggiore Hospital, Milan, Italy.

References

- 1 Cicardi M, Aberer W, Banerji A *et al.* Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014; **69**:602–16.
- 2 Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet* 1998; **351**:1693–7.
- 3 Nussberger J, Cugno M, Cicardi M. Bradykinin-mediated angioedema. *N Engl J Med* 2002; **347**:621–2.
- 4 Agostoni A, Cicardi M, Cugno M, Zingale LC, Gioffré D, Nussberger J. Angioedema due to angiotensin-converting enzyme inhibitors. *Immunopharmacology* 1999; **44**:21–5.
- 5 Pellacani A, Brunner HR, Nussberger J. Plasma kinins increase after angiotensin-converting enzyme inhibition in human subjects. *Clin Sci (Lond)* 1994; **87**:567–74.
- 6 Baş M, Greve J, Stelter K *et al.* A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med* 2015; **372**:418–25.
- 7 Colás C, Montoiro R, Fraj J, Garcés M, Cubero JL, Caballero T. Nonhistaminergic idiopathic angioedema: clinical response to icatibant. *J Investig Allergol Clin Immunol* 2012; **22**:520–1.
- 8 Stahl MC, Harris CK, Matto S, Bernstein JA. Idiopathic nonhistaminergic angioedema successfully treated with ecallantide, icatibant, and C1 esterase inhibitor replacement. *J Allergy Clin Immunol Pract* 2014; **2**:818–9.