

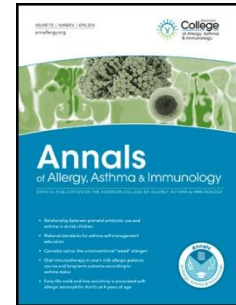
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Angioedema: systemic activation process during prodromes

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Conflicts of interest

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Key words: angioedema, high-molecular-weight kininogen, kallikrein-kinin system, kinins, kininogenase.

Abbreviations

BK-AE: bradykinin-mediated angioedema; C1Inh: C1 Inhibitor; HMWK: high-molecular-weight kininogen; KKS: kallikrein-kinin system.

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The present observation sheds new light on the pathogenesis of bradykinin-mediated angioedema by showing that local involvement occurs hours after systemic kallikrein-kinin activation. Therefore, biological diagnostic workup is of greatest value when performed at the very early phase of the attack.

Angioedema refers to the sudden, potentially life-threatening episodes of subcutaneous and/or submucosal swelling. It may be related to allergic diseases and urticaria through the release of mast cell mediators. Bradykinin-mediated angioedema (BK-AE), which is rather uncommon, does not typically respond to epinephrine, anti-histamine or corticosteroids, and obstruction of upper airways or involvement of the gastrointestinal tract may lead to life-threatening situations. BK-AE is usually caused by C1 inhibitor (C1Inh) deficiency, which is either hereditary with variants in the *SERPING1* gene (C1Inh-HAE types I and II; OMIM 106100) or acquired. BK-AE may also be linked to *F12* variants (FXII-HAE¹; OMIM: 610618) or to low kinin catabolism, *e.g.* after angiotensin-converting enzyme inhibitor intake. The cause of increased plasma bradykinin remains unknown in several cases.²

Different prodromal symptoms occurring minutes to hours prior to the BK-AE episode onset have been reported, with fatigue, discomfort and short temper as well as skin rashes, restlessness, and sadness being the most common.^{3,4}

We report here a case of BK-AE in which a kinetic study of BK production provided comprehensive insights into this syndrome. A 24-year-old woman consulted for recurrent episodes of angioedema. Attacks were always preceded by profound asthenia and involved abdominal pain, facial swelling and laryngeal edema complicated by profound respiratory acidosis on one occasion. Ethinylestradiol-based oral contraception might have contributed to the severity of the symptoms or to the triggering of the attacks. Despite injections of antihistamines, corticosteroids, and epinephrine, abdominal pain and facial edema tended to persist up to 24 hours.

Though the patient was atopic, anaphylaxis alone could not account for the entire clinical course of her AE attacks. BK-AE was then suspected, and a biological study was performed during one episode, giving the importance of biological profile to clarify the diagnosis.

The kallikrein-kinin system (KKS) was analysed on four samples taken during the prodromal period (13 hours before the attack), during the AE attack, 21 days and 6 months after the attack. This analysis included assays of kininogenase activity, C1Inh function, high-molecular-weight kininogen (HMWK) cleavage⁵ and kinin catabolism. These tests were done in the same laboratory in duplicate and repeated twice independently; samples were stored at -80°C. Oestrogen based contraception was stopped after the day-21 blood test.

Antigenic C1Inh was normal in all samples, yet its function was decreased (48.6 % of the median value) during the prodromes. Anti-C1Inh immunoblot carried out during the pre-angioedema phase showed a cleaved 95-kD protein (data not shown), indicating activation of proteases during this phase. C1Inh function improved during clinical angioedema

manifestation and remained stable 21 days and 6 months after. This transient decrease of C1Inh function is in line with earlier observations reported.

Spontaneous plasma kininogenase activity, as assayed using the Pro-Phe-Arg-*p*NA peptide⁶, strongly increased during the prodromal phase (306.9nmol/min/mL, reference <10.7nmol/min/mL). This kininogenase activity remained high during the attack, though at lower values than those observed during the prodromal phase, and returned to normal in the two post-attack samples. Plasma content of proenzymes was drastically decreased in the sample taken during the prodromal phase and recovered in the attack and post-attack samples. Prodromal and attack phases were characterized by high plasma levels of the HMWK-cleaved L-chain fragment (cLC-HK, 45-kDa, 99% and 98% respectively), in line with its sustained proteolysis by kallikrein.⁷ Cleaved HMWK levels returned to normal (<15.6%) in post-attack samples (Fig 1). Serum tryptase levels were low before and during the angioedema attack (3.65µg/L and 4.30µg/L respectively, reference <13.5µg/L), rendering a major involvement of mast cells unlikely. However, given that patient was atopic, an allergic trigger precipitating ongoing kinin system activation could not be completely ruled out.

Analysis of kinin catabolism showed normal plasma activities for aminopeptidase P, angiotensin-converting enzyme and carboxypeptidase N. The patient carried neither c.983C>A/c.983C>G mutations nor deletions encompassing exon 9 and intron 9 in *F12*.

In this kinetic study of KKS involvement during an AE attack, we showed that highest kininogenase activity, proenzyme consumption, HMWK cleavage and C1Inh function alteration occurred in the very early phase, which is during the prodromal phase. Our patient was given an early treatment plan for subsequent AE attacks and that made it difficult to reproduce the same biological conditions as in the present study. Fortunately, we had the opportunity to study another patient through an impending attack and the results were similar showing cleavage of high molecular weight kininogen 7 hours before and during visible AE

(data not shown). These findings are consistent with a systemic activation process prior to clinical expression of local angioedema, as in line with a recent model.⁸ During this early phase, C1Inh control may be overcome by sustained activation of KKS proteases, whereas it takes time for the liver to counteract this proteolytic activity by production of C1Inh and proenzymes. This could explain why the highest spontaneous kininogenase activity and lowest plasma content of proenzymes were found prior to angioedema appearance. In addition, sustained protease and long reconstitution time of HMWK could account for the persisted high HMWK cleavage observed despite proenzyme reconstitution during visible angioedema.

Finally, our results could explain why in the Icatibant Outcome Survey early treatment with this selective B2-receptor antagonist resulted in shorter attack duration.⁹ Antagonists being expected to have a pronounced efficacy when the receptors are not fully occupied by their ligands.

By showing that local BK-AE occurred many hours after systemic KKS activation, this case shed new light on the pathogenesis of the disease. The prodromal phase may occur whilst vascular permeability process progresses towards angioedema phenotype.

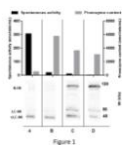
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Figure legend:

Kallikrein-kinin-system activity matched up to High-molecular-weight-kininogen molecular species, with native, N-HK; light chain, LC-HK; cleaved LC, cLC-HK. 13-hours before angioedema (A), during angioedema attack (B), 21-days post-attack (C) 6-months post-attack (D).



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