Distinct Conditions Support a Novel Classification for Bradykinin-Mediated Angio-Oedema

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Introduction

Angio-oedema (AO) refers to segmental, dermal/hypodermal oedema that resolves within a few hours or days, with multiple underlying causes and mechanisms [1]. AO is most commonly related to histamine release secondary to mast cell degranulation, which is immunoglobulin E-mediated or not [1, 2]. However, AO can also be attributable to kinin (mainly bradykinin, BK) accumulation, as is the case for prototypical hereditary AO (HAO) due to C1 inhibitor (C1-INH) deficiency [3–6]. The determination of histamine- or BK-mediated aetiology of AO based on clinical presentation may prove challenging [1]. Certain anatomical locations of AO are atypical for BK-AO may be caused by multiple inherited or acquired factors triggering BK accumulation. Therefore, we propose a novel typology for BK-AO based on the imbalance of production/catabolism of BK.

Conclusions: BK-AO may be caused by multiple inherited or acquired factors triggering BK accumulation. Therefore, we propose a novel typology for BK-AO based on the imbalance of production/catabolism of BK.

Abstract

Background: Angio-oedema (AO) can be attributable to bradykinin (BK) accumulation, as is the case for prototypical hereditary AO (HAO) due to C1 inhibitor (C1-INH) deficiency. However, our clinical experience in a reference centre has shown that some patients display a clinical history suggestive of HAO, but exhibit normal C1-INH function, have no mutation in the causative genes associated with HAO (SERPING1, F12), and report no intake of drugs known to promote AO. Objective: We sought to determine the frequency and distribution of different AO subtypes suspected to be BK-mediated AO (BK-AO) and defined by clinical, history and biological criteria (enzyme activities implicated in BK formation and catabolism). Methods: The files of all patients referred to our centre for suspected BK-AO were retrospectively analysed. Results: The distribution of patients (n = 162) was 16 and 4% with a hereditary deficiency of C1-INH or a gain of factor XII function, respectively, 29% with iatrogenic BK-AO, 21% with non-iatrogenic defective kininase activity and 30% with idiopathic increased kinin formation. Conclusion: BK-AO may be caused by multiple inherited or acquired factors triggering BK accumulation. Therefore, we propose a novel typology for BK-AO based on the imbalance of production/catabolism of BK.
histamine-mediated AO and much more common in patients with C1-INH deficiency, e.g. external genitalia, lateral aspects of the neck, abdominal wall or gastrointestinal mucosa with painful, pseudo-surgical clinical presentation [7]. C1-INH deficiency-related HAO (C1-INH-HAO) is particularly disfiguring, which may also guide the diagnosis. Finally, AO can also be classified according to its acquired (possibly iatrogenic) or hereditary nature [7, 8], assuming that the latter is exceptional for histamine-mediated AO.

Type I and II C1-INH-HAO are characterized by mutations in the SERPING1 gene [6]. Some mutations are responsible for a quantitative deficiency in C1-INH in type I and for a qualitative deficiency in C1-INH in type II [6]. However, other cases of HAO attributed to a mutation in the F12 gene (encoding factor XII) have recently been described [9] and are now referred to as FXII-HAO [10]. Their presentation is very close to that of C1-INH-HAO. In addition, acquired AO induced by anti-C1-INH auto-antibodies in the context of auto-immunity or lymphocytic proliferation (C1-INH-AAO) [6], or triggered by the intake of angiotensin I-converting enzyme inhibitors (ACEi-AAO) [11], angiotensin II receptor antagonists (AT2Ra) [12] or gliptins [13], as well as oestrogens and anti-androgens [14, 15] also exist and display a similar clinical presentation. The implication of BK in the onset of AO has been formally demonstrated only in the context of C1-INH deficiency [6]. However, acquired AO and FXII-HAO are also likely mediated by BK when considering that they rely on defective catabolism of BK (ACEi, gliptins) or increased formation of BK (gain-of-function of factor XII, acquired deficiency of C1-INH associated with oestrogen therapy or auto-antibodies). Last, the responsibility of BK in some AOs could also be supported by distinct response to treatments. Classically, C1-INH-HAO, as well as FXII-HAO or ACEi-AAO, do not respond, or only minimally respond, to H1-antihistamines (anti-H1), even at high-dose, or corticosteroids [7]. Conversely, FXII-HAO and ACEi-AAO have been shown to respond to icatibant, an antagonist of BK receptor type 2 approved for C1-INH-HAO [16, 17].

Our clinical experience in a reference centre has shown that some patients display a clinical history suggestive of HAO, but exhibit normal C1-INH function, have no mutation in the causative genes associated with HAO (SERPING1, F12) and report no intake of drugs known to promote AO. These patients often respond only poorly to high-dose anti-histamine therapies, but are sensitive to treatments more specific of BK-mediated AO (BK-AO), such as tranexamic acid or icatibant [8, 18–21]. This is in line with the concept of ‘idiopathic’ AO cases, these being often assimilated to histamine-mediated AO and treated as such [18]. However, the existence of both acquired (idiopathic non-histaminergic AAO – InH-AAO) and hereditary (HAO of unknown origin – U-HAO) has been acknowledged in the most recent classification of AO under the patronage of the European Academy of Allergy and Clinical Immunology [10]. From our side, we demonstrated that some of these AOs could be related to an increased kinin formation and/or to a decreased BK catabolism associated with a deficiency in one or several kininase(s) [15, 22–24].

Collectively, a combination of clinical items reminiscent of C1-INH-HAO (clinical presentation, response to therapeutics) could therefore be shared by several conditions and suggestive of the implication of BK in the occurrence of AO. Considering their pathophysiology, these AOs could be all assembled in a large group of BK-AO.

This study sought to determine the frequency distribution of these different conditions, suspected to be mediated by BK, in an AO patient population referred to one site of the French referral centre (CRéAK: Centre national de Référence des Angio-œdèmes à Kinines, site of Angers). In this paper we propose a BK-AO classification based on BK metabolism assessment, with its potential applications for the diagnostic and therapeutic management of BK-AO patients.

### Patients and Methods

#### Patients

This retrospective study included all patients (including children) referred to the Departments of Dermatology and Allergology of Angers University Hospital, between September 2007 and April 2012, for suspected BK-AO. Patient enrolment was based on clinical presentation and history, such as the efficacy of specific therapeutic agents (see below), as well as on biological investigation of kinin metabolism. Patients suffering from clearly histamine-mediated AO, with identification of the responsible allergen via percutaneous testing or with circulating allergen-specific immunoglobulin E antibodies, as well as those presenting with undisputable chronic spontaneous urticaria-associated AO [25] were excluded. Whenever possible, first-degree relatives were interviewed to collect their clinical history and examined to search for BK-AO and perform biological analyses.

The clinical and history criteria suggestive of BK-AO comprised the presence of recurrent AO with atypical locations for histamine-mediated AO (abdominal wall, intestine, external genitalia, etc.), along with a similar history in first-degree relatives. Urticaria, defined as pruritic, freely mobile and transient erythematous papules or plaques, was not an exclusion criterion provided that patient history and presentation were otherwise suggestive of BK-AO. We

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and others have in fact observed that the association – whether synchronous or not – with urticaria does not allow to systematically rule out the diagnosis of BK-AO [15, 26–29] (fig. 1). Recurrent urticaria (RU) was defined as the occurrence of over five urticaria episodes, and chronic urticaria (CU) as (almost) daily episodes for more than 6 weeks. Assessment of therapeutic efficacy was recorded for anti-H1 given during acute attacks or/and as prophylaxis, as well as for specific BK-AO therapeutic agents as follows: tranexamic acid given during acute attacks and/or as prophylaxis, and icatibant or C1-INH concentrate as emergency treatment during acute attacks. Anti-H1 agents were considered ineffective as prophylactic treatment if patients continued to suffer from recurrent AO despite being given a dose equivalent to three to four times the standard dose [25]. During acute attacks, tranexamic acid was administered at the minimum dose of 3 g/day for at least 2 days. Icatibant and C1-INH concentrate were prescribed at the usual doses (30 mg and 20 U/kg, respectively) for severe AO attacks and administered as soon as possible after symptom onset. The data were collected from the patients’ medical records using a standardised sheet. In cases of missing clinical data, a phone call was made to the patient or his/her attending physician.

**Biological Analyses**

The biological investigations related to C1-INH, kinin formation and kinin catabolism were carried out in the context of the FP7 ERA-Net program 2008. C1-INH analysis included quantitative and functional measurements [30]. Kinin formation was evaluated by measurement of the plasma spontaneous amidase activity using the HD-Pro-Phe-Arg-pNA substrate as recently described [24]. This assay evaluates the activity of the enzymes responsible for BK production after cleaving high-molecular weight kininogen, the serine proteases of contact phase (kallikrein, FXII). In order to investigate the kinin catabolism, the plasma activities of the three major enzymes involved in kinin degradation (kininases) were evaluated, i.e. carboxypeptidase N (CPN), angiotensin I-converting enzyme (ACE) and aminopeptidase P (APP) as previously reported [23, 31]. Whenever possible, measurements were performed in the course of an AO attack.

**Genotyping**

For the genetic investigations, DNA was extracted from the EDTA blood samples (MagNa Pure System, Roche, Meylan, France). SERPING1 gene investigation was performed by exon sequencing, and if unsuccessful by multiplex ligation-dependent probe amplification for genomic rearrangement analysis. The F12 gene was investigated through direct sequencing of exon 9 and 5′ and 3′ intron sequences as previously described [9]. Patients presenting with a deficiency of APP activity were screened for the single nucleotide polymorphism (SNP) c.-2399C>A (rs3788853) in the XPNPEP2 gene by direct sequencing [32]. Informed written consent for genetic analyses was obtained from all patients who underwent genetic investigation.

**Results**

162 patients (99 women, 63 men) with a mean age of 38 years (range 5–87) were included in the study. During the same period of time a little bit more than 4,000 patients were investigated either at the Department of Dermatology or the Department of Allergology of our University Hospital for urticaria and/or AO. Different AO subtypes were individualized (table 1).

**C1-INH-HAO**

Twenty-two patients (14%), 15 women and 7 men, presented with type I C1-INH-HAO. Their mean age was 37 years (range 5–78). Spontaneous amidase activity was increased in the 21 patients explored (nine times the median (M) value on average; 9M). Of the 20 patients investigated, 7 additionally exhibited a deficiency of one or several kinin catabolism enzymes (3 of APP, 1 of CPN and 3 of ACE). Two patients with an ACE deficiency were related (mother and daughter). One individual with a double deficiency of C1-INH and APP, detected in the course of a family investigation, was asymptomatic. Two female patients worsened following intake of postmenopausal hormone replacement therapy in one case and oestrogen-progestin pill in the other. Four patients (18% of this group) presented with RU. Four patients (2%), 3 women and 1 man, suffered from type II C1-INH-HAO. Their mean age was 44 years (range 7–84). Spontaneous ami-
dase activity, measured in 3 patients, was found increased in all of them (3M on average). Kinin catabolism was not investigated in this patient group. No aggravating drugs were found. Two patients presented with RU.

**FXII-HAO**

Seven patients (4%), 4 women and 3 men, suffered from AO associated to the p.Thr328Lys mutation in the F12 gene. Their mean age was 28 years (range 6–60). Spontaneous amidase activity was increased in the 6 patients explored (2M on average). The only symptomatic male patient, who was 6 years of age, suffered from abdominal attacks and had an increased spontaneous amidase activity. The 5 patients investigated exhibited normal kinin catabolism. Three patients responded to tranexamic acid administered for acute attacks, and 2 patients responded to tranexamic acid administered as prophylactic treatment. Icatibant therapy was required in 1 patient and proved effective. One patient presented with RU.

**C1-INH-AAO**

Three patients (2%), 2 women and 1 man, exhibited AO due to acquired C1-INH deficiency. The diagnosis of AAO was suspected in the presence of non-familial, late-onset AO and confirmed by anti-C1-INH antibodies and the absence of a mutation in the SERPING1 gene. The mean age was 73 years (range 65–87). Spontaneous amidase activity was increased in the 2 patients explored (25M on average). Kinin catabolism was normal for the 2 patients investigated. In 1 patient, AO attacks were hastened by AT2Ra intake. None presented with urticaria.

**Drug-Induced AO in Patients with Normal C1-INH and No F12 Gene Mutation**

Six patients (3%), 2 women and 4 men, were affected by AO induced by an ACEi or an AT2Ra. Their mean age was 78 years (range 68–89). The mean time between treatment initiation and first AO episode was 11 years (range 6 months to 17 years). Spontaneous amidase activity was increased (3M) in 1 of the 5 patients explored. A kinin catabolism deficiency was detected in 5 patients: 2 exhibited ACE deficiency and 3 APP deficiency associated to the SNP c.-2399C>A of the XPNPEP2 gene. For both patients, low ACE activity was related to ACEi intake, and AO had resolved 3 months after the responsible treatment was discontinued. One patient responded to tranexamic acid administered during acute attacks. Icatibant was not required in any patient. None presented with urticaria.

Forty-three patients (27%), 41 women and 2 men, had AO induced by hormone therapy. In 29 cases, this was associated with a transient and limited decrease of C1-INH function, and in 24 cases with an additional C1-INH protein cleavage detected by immunoblot analysis. Both anomalies were reversible upon treatment discontinuation, as previously described [14, 15]. The mean patient age was 33 years (range 13–77). In women, 39 cases were induced by an oestrogen-progestin pill, 1 by raloxifene and 1 by royal jelly, which is known to be rich in phyto-oestrogens. The mean time between contraceptive intake and AO occurrence was 8 years (range 6 months to 27 years). The most commonly incriminated contraceptives combined ethinyl estradiol 35 μg and cyproterone acetate 2 mg, or ethinyl estradiol 30–40 μg and levonorgestrel 0.15–0.20 mg. The time between raloxifene intake and AO occurrence was 7 years and that between royal jelly

### Table 1. Distribution of different conditions of BK-AO in patients admitted to a French reference centre

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean age, years</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>38</td>
<td>99 (62%)</td>
<td>63 (38%)</td>
<td>162 (100%)</td>
</tr>
<tr>
<td>Type I C1-INH deficiency</td>
<td>37</td>
<td>15 (68%)</td>
<td>7 (32%)</td>
<td>22 (14%)</td>
</tr>
<tr>
<td>Type II C1-INH deficiency</td>
<td>44</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Factor XII mutation carriage</td>
<td>28</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Acquired C1-INH deficiency</td>
<td>73</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Iatrogenic BK-AO (ACEi, AT2Ra)</td>
<td>78</td>
<td>2 (33%)</td>
<td>4 (67%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Iatrogenic BK-AO (hormone therapies)</td>
<td>33</td>
<td>41 (95%)</td>
<td>2 (5%)</td>
<td>43 (25%)</td>
</tr>
<tr>
<td>Kinin catabolism deficiency</td>
<td>40</td>
<td>19 (56%)</td>
<td>15 (44%)</td>
<td>34 (21%)</td>
</tr>
<tr>
<td>Increased amidase activity without C1-INH deficiency or F12 mutation</td>
<td>34</td>
<td>16 (33%)</td>
<td>32 (67%)</td>
<td>48 (30%)</td>
</tr>
<tr>
<td>BK-AO with no biological abnormality identified</td>
<td>45</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
<td>10 (6%)</td>
</tr>
</tbody>
</table>

Some patients combined several conditions, therefore total percentages may exceed 100%.
intake and AO occurrence 1 month. Spontaneous amidase activity was increased (3M on average) in 23 of the 38 patients explored. For 21 patients, enzymatic activity was restored to normal within 3–6 months after hormone withdrawal. Kinin catabolism was impaired in 9 of the 11 patients investigated: in 1 patient for APP activity, in 5 for CPN and in 5 for ACE. Among the 17 patients who were given tranexamic acid, 12 responded to prophylactic treatment and 9 to in-demand treatment for acute attacks. In one case, C1-INH concentrate therapy was required for a laryngeal attack and proved effective. Icatibant was not used by any patient. Urticaria was present in 16 patients (37% of this group), with 9 RU and 7 CU cases. All patients were advised not to resume oestrogen-based contraceptives but rather to use progestin-only contraceptives as recently suggested [33]. Three patients exhibited AO recurrence after the incriminated treatment was stopped, 1 during pregnancy and the 2 others during ovarian stimulation for infertility. For 24 patients, AO manifestations were searched for in first-degree relatives, with a positive result in 8 cases. The cases that occurred in men were associated with either finasteride use for androgenetic alopecia or diethylstilbestrol use for prostate cancer. The time between finasteride use and AO occurrence was 3 years and that between diethylstilbestrol intake and AO occurrence was 6 months.

**AO in Patients with Normal C1-INH and a Deficiency of One or Several Kininases**

In total, 34 patients (21%), 19 women and 15 men, had a kinin catabolism deficiency, with enzymatic activities out of the low reference value. Their mean age was 40 years (range 8–70). Of these, 10 displayed CPN (fig. 2), 15 APP and 12 ACE deficiency. In 12 patients, the low APP activity was associated with the SNP c.-2399C>A of the XPNPEP2 gene. Spontaneous amidase activity was additionally increased (3M on average) in 13 of the 34 patients. In 11 cases, AO was worsened by drug intake, namely oestrogen-progestin pill in 8 patients, ACEi in 1, AT2Ra in 1 and diethylstilbestrol in the remaining one. In 6 patients the family history was positive in first-degree relatives. Of the 23 patients given tranexamic acid, 19 responded during acute attacks and/or as prophylaxis, 7 during acute attacks and 18 as prophylaxis. Icatibant injection was required in 6 cases and effective in 3 of them. In 3 cases, C1-INH concentrate therapy was administered, showing efficacy in 2. In 1 case, neither icatibant nor C1-INH concentrate proved effective in the context of abdominal pain and AO involving the lower face. Thirteen patients (38%) presented with urticaria consisting of RU in 8 and CU in 5.

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**Fig. 2.** Facial AO in a 6-year-old boy with CPN deficiency. The boy experienced recurrent AO attacks as well as urticaria. Note the slightly erythematous character of the oedema. Anti-histamines were ineffective, but tranexamic acid proved effective as a prophylaxis. CPN plasma values were 28 and 31 nmol/min/ml (normal 35–55) on two independent evaluations. Spontaneous amidase activity was unremarkable.

**Fig. 3.** Voluminous AO in a 42-year-old patient. Facial disfigurement and ineffectiveness of high-dose anti-histamines and steroids (on demand or on a prophylactic basis) supported the diagnosis of BK-AO. Tranexamic acid proved promptly effective. However, no abnormalities were found after several investigations of BK metabolism. The F12 gene was unaltered. This patient reported a single episode of penile urticaria.
AO Associated with an Increased Spontaneous Amidase Activity but Normal C1-INH and No FXII Gain-of-Function

Forty-eight patients (30%), 16 women and 32 men, exhibited increased kinin formation (2M on average). Their mean age was 34 years (range 7–70). Kinin catabolism was reduced in 11 of the 48 patients: APP activity in 6, ACE in 3 and CPN in 2. In 16 patients, family history of AO was positive in first-degree relatives. Among the 27 patients given tranexamic acid, 26 responded during acute attacks and/or as prophylaxis. In the 3 patients receiving icatibant, treatment response was satisfactory. Among the 46 patients assessed, urticaria was present in 14 (30% of this group), namely CU in 5 and RU in 9.

AO without Any Biological Abnormality Identified

Ten patients (6%), 7 women and 3 men (fig. 3), did not exhibit any biological abnormalities. Their mean age was 45 years (range 16–66). CU was found in 1 of these cases.

Discussion

According to the recent classification of AO without wheals [10], many cases, both acquired and hereditary, could be registered in the groups of AO with unknown cause (INH-HAO and U-HAO). Our observations give consistent arguments to dismantle this group using an aetiopathological definition based on new biological findings. Over a 4-year period, we enrolled 162 patients likely to qualify for a BK-AO diagnosis based on clinical and history criteria. Among them, only 42 (26%) displayed ‘classical’ types of BK-AO (C1-INH-HAO, FXII-HAO, C1-INH-AAO, ACEi-AAO). In addition to the medical history and clinical presentation compatible with ‘classical’ BK-AO, though generally less serious, the diagnosis was supported by biological dysfunction of the BK metabolism in most of the remaining patients [23, 24]. The majority of these AO responded to tranexamic acid given as prophylaxis and/or as on-demand therapy during acute attacks, with disease recurrence observed following dose reduction, as previously reported [15].

Study limitations exist in our work, particularly because some data are lacking due to the retrospective design. In addition, we have for years shown a special interest in AO occurring in the absence of C1-INH deficiency. This has certainly introduced a recruitment bias and subsequent over-evaluation of the frequency of these cases. We believe however that BK-AO is actually a syndromic condition caused by multiple, inherited or acquired, factors that are often combined to determine both the onset of AO and occurrence of attacks [23, 31, 34]. These factors may determine increased BK production and/or decreased BK catabolism in a synergistic fashion, and/or interact with kinin receptors or with drugs targeting the kinin metabolism. The family histories of some cases support still unidentified genetic abnormalities that are expected to increase the susceptibility to AO-BK [8, 21, 33]. In this respect, changes in BK receptors or uninvestigated kininases (e.g. dipeptidyl peptidase IV) should be evaluated. Our findings support a comprehensive classification of BK-AO based on the imbalance between kinin production and degradation, assessed via plasma amidase and kininase activity measurements, respectively. This proposal is summarized in table 1.

In the symptomatic patients with identified type I C1-INH-HAO, spontaneous amidase activity was constantly increased, even between attacks. This observation is consistent with a contact phase activation and kinin overproduction in the situation of defective control by C1-INH [35] and confirms the value of this assay for deciphering BK-AO in symptomatic patients [24]. Seven patients (only 4% of the investigated population) displayed FXII-HAO associated with the pThr328Lys mutation in the F12 gene. This mutation, even frequent compared to the other F12 gene causative mutations identified, is a low prevalent gene defect [8, 9, 21]. In symptomatic F12 mutation carriers, we always observed increased spontaneous amidase activity, again supporting the concept that increased kinin formation would be indicative of disease occurrence [24]. In addition to oestrogen intake, the clinical presentation of these AOs could be strongly influenced by a low BK catabolism depending on ACE activity, a situation distinct from that observed for C1-INH-HAO depending on APP activity [23, 31, 33].

In our series 41 patients, i.e., nearly 25% of the study population, displayed AO induced by hormone therapy. Ten years after its first description [14, 15], this BK-AO subtype remains poorly understood. The condition is characterized by partial C1-INH cleavage, associated with a moderately decreased C1-INH function, along with an increased plasma spontaneous amidase activity in most patients [15]. Clinically, these patients express a less severe phenotype than those with profound C1-INH deficiency due to a SERPING1 mutation. To our knowledge there is, however, no established correlation between the extent of C1-INH function decrease and the clinical phenotype severity. Twelve female patients exhibited neither C1-INH dysfunction nor C1-INH cleavage. Several hypotheses can be raised. Investigation of C1-INH may have
been performed out of an AO attack or while the patient was already treated with tranexamic acid, with subsequent control of plasma amidase activity. In line with Saule et al. [33], we systematically recommended progestin-only contraceptives to the patients still wanting to use hormone-based contraception. However, two patients exhibited disease recurrence during ovarian stimulations and another one during pregnancy. Physicians should therefore remain cautious with respect to the prescription of hormones in this context and should suggest appropriate clinical and biological monitoring of pregnancy. Of the two men included in this group, one developed AO after using finasteride (5α-reductase inhibitor) that was prescribed for androgenetic alopecia. This potentially severe adverse effect must be known by dermatologists. Its clinical presentation is reminiscent of AO observed during dutasteride therapy prescribed for benign prostatic hyperplasia [36].

In total, 34 patients exhibited a deficiency of the enzymes involved in kinin catabolism. Two of the 6 patients exhibiting AO under ACEi also had an APP deficiency. The latter condition could thus be a predictor of AO occurring during ACEi treatment [37–39]. Nine patients displayed CPN deficiency, which has been rarely reported in the literature. Matthews et al. described a family with autosomal recessive CPN deficiency [40, 41]. The deficiencies of the enzymes of the kinin catabolism are predictive factors of occurrence or seriousness of C1-INH-HAO or ACEi-AAO, but our results show that, by themselves, these enzyme defects could also be able to precipitate AO. The compensation of one of the redundant enzymes by another could be a possible hypothesis for the usually lower severity than that observed in C1-INH-HAO.

We found that BK-AO may be associated with RU or CU (73 patients, 44% in this series). Six patients with a genetically confirmed type I/II C1-INH-HAO also exhibited RU (fig. 1). If confirmed in additional studies, our findings would imply that a diagnosis of BK-AO should not be excluded on the basis of urticaria according to patient history or physical examination. Our observations contrast with guidelines in which absence of RU or CU was described as a central feature of BK-AO [6]. An association between urticaria and BK-AO has previously been reported in BK-AO unrelated to C1-INH deficiency [15, 27–29]. The pathophysiology of these urticarial rashes, which may either occur at the prodromal AO stage or at times in a chronologically independent way, remains poorly understood in the context of BK-mediated disease. Fortuitous co-occurrence may be proposed as an explanation for our observations; however, the rate of urticaria among all subtypes of BK-AO in our study is substantially higher than in the general population, suggesting a shared pathogenesis. Urticaria and BK-AO co-occurrence could rely on kinin formation by mast cells, by contact-phase activation by heparin [42] or tryptase [43], or by BK receptor-mediated mast cell activation [44]. Interestingly, Na et al. [45] observed that the oral intake or topical application of tranexamic acid reduced the number of cutaneous mast cells, which may explain the efficacy of this drug in certain BK-AOs.

In conclusion, our work provides new insights for hereditary or acquired AO of unknown origin. Our findings support the evidence that, in some patients, the pathophysiology of AO could be mediated, at least in part, by BK as supported by enzymatic tests. In some cases, it is even likely that several changes in BK metabolism are combined to determine the onset of BK-AO. Additional research is necessary to further characterize AO unrelated to C1-INH deficiency and to confirm concomitant urticaria as a frequent finding in the setting of BK-AO.

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Disclosure Statement

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