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EDITORIAL

Prediction and prevention of ACE-inhibitor-induced angioedema—an unmet clinical need in management of hypertension

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ACE inhibitor (ACE-I)-induced angioedema, with an underreported incidence of 0.1–0.7%, manifests as non-pitting oedema of subcutaneous and submucosal tissues. It becomes life-threatening when involving the larynx. Main risk factors include Black African and Hispanic descent, female gender, age, being a smoker, and a history of ACE-I-induced cough. In most cases the management is based on discontinuation of ACE-I and offering an alternative antihypertensive treatment (e.g., an angiotensin II receptor blocker, i.e., ARB). The discovery of single nucleotide polymorphisms (SNP) (e.g., a variant rs34485356 located upstream from the Bradykinin receptor B2 gene on chromosome 14), offers a promise of developing genotype-informed approaches for early prediction and effective prevention.

Keywords ACE-I-induced angioedema · Side-effect · Pharmacogenomics · Personalized Medicine · Hypertension

Introduction

Angioedema, characterized by asymmetric non-pitting edema affecting the subcutaneous and submucosal layers of tissue, often becomes life-threatening when it involves larynx. The incidence rate of angioedema associated with ACE inhibitors (ACE-I) varies between 0.1 and 0.7%, which is probably an underestimate [1, 2]. Indeed, 20–40% of all visits to emergency department due to angioedema each year are attributed to ACE-I [3] and the hospitalization rates for angioedema increased due to the increasing use of ACE-I [4]. Yet, this important clinical complication of antihypertensive treatment is barely mentioned in clinical guidelines on management of hypertension. The prospective advent of personalized medicine is tailoring treatment for hypertensive patients to their individual clinical profiles. In this context, identifying those who need an ACE-I but show an elevated risk for ACE-I-induced angioedema could lead to choosing for example, angiotensin receptor blockers (ARBs) (which do not share the same angioedema-associated risk with ACE-I over the latter) [5–7].

Pathogenesis of ACE inhibitor-induced Angioedema

ACE-I not only inhibit the conversion of angiotensin I into angiotensin II (within the classical arm of the renin-angiotensin system) but also influence bradykinin. Bradykinin's degradation is carried out by several enzymes: angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), aminopeptidase P (APP), dipeptidyl peptidase IV (DPP-IV), and kininase I [8]. When ACE is inhibited, bradykinin degradation is altered. Upon binding to its receptor, bradykinin B2 receptor (B2R), bradykinin stimulates the release of nitric oxide, substance P, prostacyclin, and endothelium-derived hyperpolarizing factor, which enhance vascular permeability [9]. This increased permeability is a key biological characteristic of angioedema. Substance P, another vasodilator peptide degraded by ACE, operates through the neurokinin 1 (NK1) receptor. Studies have shown that the degradation half-life of substance P is lower in ACE-I patients with a history of angioedema compared to those without [10]. Intriguingly, only a relatively small proportion of patients who are prescribed ACE-I develop this side effect, suggesting that there is a degree of inter-individual variation in susceptibility to angioedema driven by ACE-I.

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Presentation features

Contrary to popular belief, the onset of angioedema does not necessarily occur in the first week of ACE-I treatment. In many instances, the adverse effects manifest much later—weeks, months, or even years after the introduction of the medication which means that the risk must be considered as a persistent risk in patients taking ACE-I [11]. Clinical manifestations also vary widely, ranging from non-itchy [12] localized swelling of the face, tongue, lips (see Fig. 1), throat, or larynx and sometimes—the gut (mimicking irritable bowel syndrome or ischemic colitis). Notably, laboratory tests have limited (if any) value in the diagnosis; this is largely based on the history and clinical examination. While most cases present mild symptoms, severe complications, including asphyxiation, have been reported [13]. Angioedema recurrence is common among patients who continue ACE-I treatment, with subsequent episodes often presenting more severe symptoms [14]. Some patients may experience multiple episodes before the condition is accurately diagnosed. Angioedema is not a dose-dependent side effect of ACE-I.

Unpacking the risk factors

Various demographic and clinical characteristics heighten the risk for ACE-I-induced angioedema. People of Black African and Hispanic descent have an increased risk of this condition [2, 14–16]. Women, individuals aged over 65 years, and patients on immunosuppression [17] also face elevated risks. Interestingly, those with a prior history of angioedema, smokers, and individuals with a history of ACE-I-induced cough (which itself corresponds to a nine-fold increase in the risk) are more susceptible [1]. The risk further multiplies (4–5 times) with co-treatment of Dipeptidyl peptidase IV inhibitors [8, 18]. The recent Mendelian randomization (MR analyses) further revealed that chronic obstructive pulmonary disease and history of allergy appeared to increase the risk for ACE-I–induced angioedema [19].

The genetic angle

Several hereditary angioedema genes [serpin Family G Member 1 gene (*SERPING1*), coagulation factor XII gene (*F12*), angiopoietin 1 gene (*ANGPT1*), plasminogen gene (*PLG*), and kininogen 1 gene (*KNG1*)] have been investigated as potential contributors to variation in individual susceptibility to ACE-I-induced angioedema; the evidence so far suggests this is not the case [20]. An initial genome-wide association study (GWAS) carried out in the United States did not discover any genome-wide significant associations [21]. A larger, more comprehensive GWAS conducted in a Swedish cohort have identified several candidate genes [22]. Specifically, Bradykinin receptor B2 gene (*BDKRB2*), ETS Variant Transcription Factor 6 gene (*ETV6*), Membrane Metalloendopeptidase gene (*MME*), and Protein Kinase C Theta gene (*PRKCQ*) demonstrated nominal associations ($p < 0.05$) with angioedema but failed to pass the stringent Bonferroni correction for multiple testing. Intronic variants in the Potassium Calcium-Activated Channel Subfamily M Alpha 1 gene (*KCNMA1*) gene on chromosome 10 were identified with genome-wide significance ($p < 5 \times 10^{-8}$) but were not replicated in an independent cohort. A whole-exome study found a non-replicated association between ACE-I-induced angioedema and a variant in the factor V leiden (*F5*) gene [23].

A substantial leap in our understanding of ACE-I-induced angioedema has been achieved through the recent GWAS conducted in European cohorts from the Copenhagen Hospital Biobank and Swedegene [19]. A single nucleotide polymorphism (SNP) located 60 kb upstream from the *BDKRB2* on chromosome 14q32.2 (rs34485356), has emerged as a locus significantly associated with this condition with an odds ratio (OR) of 1.62 (95% CI: 1.38–1.90; $P = 4.3 \times 10^{-9}$). An independent replication cohort yielded a highly similar OR. These findings have not been replicated in non-European populations yet.

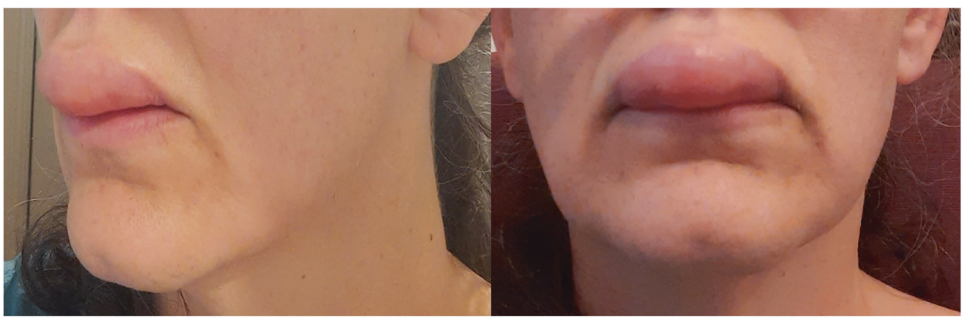

Fig. 1 Recurrent ACE-I-induced angioedema manifesting as a localized non-itchy swelling of the upper lip in 53-year old woman treated with ramipril 10 mg/day. Reproduced with the patient's permission

Treatment modalities

In the treatment of acute and severe cases of angioedema associated with ACE-I, immediate attention is often required, especially if there is a respiratory compromise. Intubation may be necessary in these situations to ensure an open airway. Traditional medications such as antihistamines, epinephrine, and glucocorticoids are generally not very effective because the underlying mechanism is driven by the accumulation of bradykinin rather than histamine. However, fresh frozen plasma and bradykinin receptor antagonists like icatibant [24] have shown some promise [1]. For non-severe cases, the first step is to discontinue the ACE-I. Patients should not be re-challenged with an ACE-I, especially if there is diagnostic uncertainty, nor should another ACE-I be introduced due to the class effect. Patient education and information are crucial, including the risks of returning to any form of ACE-I treatment [1]. Switching to other blood pressure-lowering medications, like ARBs, should be considered. Indeed, ARBs did not show a significant increase in the risk for serious angioedema [7]. In fact, the hazard ratios of angioedema and severe angioedema on ARBs were comparable to β-blockers [7] making ARBs a safer alternative for those with history of ACE-I-induced angioedema [7]. The risk of angioedema and severe angioedema with aliskiren use was ~3–8 times higher than with β-blockers [7]. While these estimates may have been influenced by very small numbers of cases, aliskiren is not considered a safe replacement option for ACE-I in those with history of ACE-I-induced angioedema.

Personalized medicine: genomics to guide a prediction and prevention

The emergence of "replicated" genetic variants associated with ACE-I-induced angioedema in GWAS (e.g., rs34485356) suggests a potential for development of genotype-informed approach in predicting and preventing this serious adverse effect of antihypertensive treatment. The predictive value of a single variant associated with angioedema in GWAS is of course limited due to complex, heterogenous and possibly polygenic nature of this condition. Therefore, the discovery of additional credible genetic determinants through larger GWAS and their subsequent triangulation in genetic risk scores is necessary. It is absolutely critical that such studies are conducted in populations of different ancestries inclusive of these with the highest risk of ACE-I-induced angioedema. Indeed, genetic information (possibly integrated with other key clinical variables) holds the promise of enhanced prediction and prevention of side effects of antihypertensive treatment through e.g., therapeutic decision-making [25] (Box 1).

Box 1 Proposed strategies for minimizing angioedema risk in ACE inhibitor therapy in the future

1. Multi-factorial risk assessment: A predictive algorithm incorporating genetic, environmental, and clinical variables should be developed to guide clinicians in personalized drug prescription.
2. ARBs as an alternative: For patients with (i) history of ACE-I-induced angioedema, (ii) history of ACE-I-induced cough, (iii) risk factors for angioedema, ARBs could serve as a safer therapeutic alternative in case there is a compelling evidence of the need to block renin-angiotensin system
3. Ethnic-specific considerations: Given consistently higher risk of ACE-I-induced angioedema in patients of African and Hispanic ethnicity future guidelines could recommend ethnicity-based risk assessments and consideration of ARBs versus ACE-I.
4. Future direction for pre-emptive Genetic Screening: The relevance of pre-emptive genetic tests, may be established once supported by further, more extensive multi-ethnic GWAS studies.

ACE-I : ACE inhibitors.
ARBs : angiotensin receptor blockers.

Summary

Accurate prediction of ACE-I-induced angioedema remains a pressing need in the field of hypertension management. A clinical tool assessing the risk of ACE-I-induced angioedema would help clinicians to make appropriate clinical choices and could be potentially life-saving (for example, through choosing some of already available antihypertensive drugs that do not increase the risk of angioedema in patients who are particularly susceptible to it). It is likely that genetic information could make important contributions to such asessements and decisions. Therefore, further progress in pharmacogenomics is essential for uncovering the identity of key genetic drivers associated with ACE-I-induced angioedema.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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