CASE REPORT

Recurrent angioedema associated with pharmacological inhibition of dipeptidyl peptidase IV

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SUMMARY

Angioedema (AE) of the upper airways is a severe and potentially life-threatening condition. The incidence has been increasing in the past two decades, primarily due to increased use of medications inhibiting the degradation of vasoactive peptides. Acquired angioedema related to angiotensin-converting enzyme inhibitors (ACEI-AAE) is well known, but other pharmaceutical agents also affect the degradation of bradykinin and substance P. We present a middle-aged man with recurrent episodes of severe AE of the oral cavity, hypopharynx and larynx due to pharmacological inhibition of dipeptidyl peptidase IV.

BACKGROUND

Angioedema (AE) is a transient swelling of the subcutaneous tissue and/or submucosa. When attacks involve the upper airways, asphyxiation can occur. The most common type of AE is idiopathic AE (IAE); however, histamine-mediated allergic and anaphylactic AE is also well known. Less known are conditions in which excessive levels of other vasoactive peptides such as bradykinin and substance P lead to extravasation of plasma.^{1 2} Non-histaminergic AE includes hereditary AE (HAE) and acquired AE (AAE); IAE may also be bradykinin-mediated. The incidence of non-histaminergic AE has increased for the last two decades; primarily due to continuous increase in the prescription of medications that inhibit the degradation of bradykinin and substance P.³ Angiotensin-converting enzyme inhibitors (ACEI) are prescribed to patients with hypertension and/or renal disease to lower the blood pressure through an inhibition of angiotensin-converting enzyme (ACE). This enzyme is also partly responsible for the degradation of bradykinin and substance P to inactive molecules.⁴ More than 40 million people worldwide are treated with an ACEI, and the incidence of ACEI-induced angioedema (ACEI-AAE) is reported to be up to 2%.^{2 3 5}

Diabetes—especially type 2 diabetes mellitus—is a growing worldwide challenge with 422 million people diagnosed with type 1 or type 2 diabetes in 2014.⁶ Diabetes is treated with insulin or oral antidiabetics (eg, biguanides, sulfonylurea, meglitinides and glitazones). Furthermore, a new and effective class of oral antidiabetic drugs, ‘gliptins’, was recently introduced. They function by a competitive inhibition of the enzyme dipeptidyl peptidase IV (DPP-IV), which leads to higher postprandial levels of insulin and lower levels of glucagon and thus a lower blood sugar level.⁷ DPP-IV is also

involved in the degradation of other peptides, including bradykinin and substance P.^{8 9} Substance P contributes to tracheal ACEI-AAE in animal models through binding to the neurokinin 1 receptor (NK1).¹⁰ Also neuropeptide Y and B-type natriuretic peptide are substrates for DPP-IV. These neuropeptides are involved in cardiovascular homeostasis, angiogenesis, cell proliferation, migration and differentiation but are not known to contribute to the development of non-inflammatory AE.¹¹ However, neuropeptide Y can elicit inflammatory paw oedema in rats and, to a minor extent, increase the permeability of the microvasculature in the skin of murine models.^{12 13} AE is a rare adverse reaction to DPP-IV inhibitors, probably because ACE will usually degrade bradykinin and substance P. In patients treated with an ACEI and a DPP-IV inhibitor, the level of bradykinin and substance P might increase and lead to a significant higher risk of AE, since aminopeptidase B, neutral endopeptidase and carboxypeptidase N in predisposed individuals are not sufficient for degradation of bradykinin and substance P (figure 1).^{4 14} Furthermore, the nervous system might play some role, as substance P in response to bradykinin, tissue trauma or other proinflammatory mediators, is released from specific nerve endings.¹⁵ Knowledge of the interaction between DPP-IV inhibitors and ACEI is crucial when dealing with AE patients, as the number of patients treated with these drugs is increasing and because the condition is potentially lethal.¹⁶ Patients with a known predisposition to non-histaminergic AE should be carefully advised when choosing an antidiabetic drug. ACEI is contraindicated in patients with HAE, and DPP-IV inhibitors should only be used with utmost care in these patients.¹⁷

CASE PRESENTATION

A middle-aged Caucasian male with no history of allergy or AE presented with repeating episodes of spontaneous swelling in the head and neck area. On several occasions, the patient was referred to the local emergency department with severe swelling of the tongue and the larynx but with no other allergic symptoms (pruritus, urticaria, hypotension, vomiting or bronchospasm). The treatment consisted initially of intravenous antihistamines and corticosteroids but had no effect. He had no or sparse efficacy of epinephrine, but nevertheless was instructed to self-inject this medication with an epinephrine-pen at home in case of swellings. On one occasion, complement C1-inhibitor concentrate (Berinert) was administered with some

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Figure 1 Bradykinin and substance P release and degradation with pharmacological inhibition of ACE and DPP-IV. High molecular weight kallikrein (HK) is cleaved by plasma kallikrein to form bradykinin. Bradykinin stimulates substance P release through binding to bradykinin-2 receptors (B2 receptors) on sensory nerve ends. Aminopeptidase P, neutral endopeptidase and carboxypeptidase N are in predisposed individuals not sufficient for degradation of bradykinin and substance P, thus, ACE-inhibition and DPP-IV inhibition lead to increased levels of bradykinin and substance P and which causes an increased risk of angioedema. ACE, angiotensin-converting enzyme; DPP-IV, dipeptidyl peptidase IV.

effect. It was determined that since August 2012 the patient was taking an ACEI (Ramipril) as an antihypertensive drug on a daily basis and, thus, ACEI-AAE was suspected. Even though the ACEI was discontinued, the patient continued to experience AE with severe oral, hypopharyngeal and laryngeal attacks. His travelling insurance limited their coverage due to the severity of the AE, so he was prevented from travelling abroad.

The patient was referred for further evaluation to the Department of Dermatology and Allergy Centre at Odense University Hospital, which holds the position of Global Centre of Excellence within the field of anaphylaxis, as he had recurrent AE reaching 47 attacks within a year. In a few episodes, the swellings had been associated with ingestion of rye bread and therefore an allergic reaction was suspected. All tests for allergy (skin prick tests and histamine release tests) were negative, and the swellings did not respond to several types of anti-allergic medication (high dose antihistamines, corticosteroids and epinephrine). To exclude HAE or AAE, complement tests were performed with normal results. The patient was concurrently included in the PREDICTION-ADR project regarding genetic polymorphisms and ACEI-AAE (<http://www.prediction-adr.eu/>). At a follow-up telephone interview, it was established that just days before the first swelling episode, the patient had visited his general practitioner to adjust his antidiabetic treatment and had started daily treatment with a DPP-IV inhibitor (sitagliptin, Januvia). Owing to suspected DPP-IV induced AE, he was advised to change this treatment and was substituted with (empagliflozin, Jardiance). Since discontinuation the patient has had only two minor swellings of the tongue, neither requiring hospital admission (observation period 12 months). At his last outpatient visit, the condition was considered fully remitted and the patient's hospital course was terminated.

INVESTIGATIONS

Biochemistry during a severe AE attack:

- ▶ C reactive peptide: 6 mg/L (< 6 mg/L).
 - ▶ White blood cell count: $11.1 \times 10^9/L$ ($3.5-8.8 \times 10^9/L$).
 - ▶ Neutrophils: $8.2 \times 10^9/L$ ($1.5-7.5 \times 10^9/L$).
 - ▶ Kidney and liver function were normal.
- Other tests performed when no AE was apparent:
- ▶ Histamin release test for autoimmune urticaria: negative.
 - ▶ Skin prick test with standard inhalation panel, food panel and selected grains: small positive reaction to weed with no relevance.
 - ▶ Complement levels: C1 inhibitor activity 121% (70–130%).

DIFFERENTIAL DIAGNOSIS

HAE

Onset of AE episodes is usually in childhood or early adulthood. Levels of total complement C1-inhibitor or activity would be low. Symptoms also include erythema marginatum and recurrent abdominal pain.

AAE

Complement C1-inhibitor levels would be low due to high degradation rates of the protein; usually occurs in patients with a clonal lymphoproliferative disease.

IAE

Some cases can be similar to the described case, but most cases are associated with urticaria, and many patients respond to traditional antiallergic therapy with high dose antihistamines, corticosteroids and epinephrine.

Type I allergy

Other symptoms of allergy such as rhinoconjunctivitis, bronchospasm, nausea, hypotension vomiting, diarrhoea and abdominal pain and urticarial rash will usually be present.

ACEI-AAE

Often presents itself with isolated AE in the head and neck area and is caused by inhibition of ACE. This type of AE is presumed to be mediated by bradykinin and substance P and responds to drugs interfering with bradykinin metabolism and action. Patients with ACEI-AAE might continue to have attacks after withdrawal of culprit drug, but usually less severe and less frequent.

TREATMENT

Antiallergic treatment with high dose antihistamines, corticosteroids, epinephrine and complement C1-inhibitor concentrate (Berinert) were ineffective when used. Withdrawal of DPP-IV inhibitor markedly improved his condition.

OUTCOME AND FOLLOW-UP

During a 12-month follow-up period, the patient has had two episodes with slight swelling of the upper lip and tongue (respectively) compared to 47 attacks in a year while treated with the DPP-IV inhibitor. The patient's travel insurance has again approved him to travel outside of Denmark.

DISCUSSION

ACE is the major enzyme responsible for the degradation of bradykinin and substance P. DPP-IV plays a minor role in the degradation of the vasoactive peptides when ACE is present and fully functioning. When ACE is inhibited, as in patients

treated with an ACEI, DPP-IV is the main degrading enzyme of bradykinin and substance P.^{4 10 14} In the above case, the patient received ACE and DPP-IV inhibitors simultaneously, causing both of these enzymes to be inhibited, potentially resulting in increased levels of the vasoactive peptides bradykinin and substance P. AE attacks started only when a DPP-IV inhibitor was added to ACEI and continued even after ACEI discontinuation. Although ACE should regain its function after a few days, it is known from the literature and clinical practice that patients with ACEI-AAE may continue to have (milder) swellings several months or even years after discontinuing ACEI treatment.¹⁸ This suggests a prolonged subnormal function of ACE or an underlying idiopathic swelling tendency (IAE). After discontinuation of DPP-IV inhibitor treatment, there were only two minor episodes with AE indicating that the degradation of bradykinin and substance P was performed mainly by DPP-IV. However, the exact pathophysiological mechanism needs more clarification. Other peptides are also affected by DPP-IV inhibition that is, neuropeptide Y, which can elicit inflammatory paw oedema in rats. Also, a minor increase in the permeability of the microvasculature in murine models has been observed. If the degradation of these peptides is inhibited by DPP-IV inhibitors, the levels could increase to such an extent that they contribute to the development of AE; however, future studies are needed to clarify this effect.^{12 13} A previous study has suggested a protective effect in persons with diabetes on ACEI-AAE due to increased levels of DPP-IV; however, this protective effect is diminished once DPP-IV inhibitors are used.^{19 20}

Patient's perspective

I hope you will distribute the knowledge on this disease, as I have encountered many healthcare personnel with none or very little knowledge in the field. This has been very frustrating. (Translated from Danish)

Learning points

- Acquired angioedema related to angiotensin-converting enzyme inhibitor (ACEI-AAE) is the most common drug-induced AE.
- AAE related to dipeptidyl peptidase IV (DPP-IV) is a new type of iatrogenic AE.
- Concomitant ACEI and DPP-IV inhibitor therapy theoretically leads to a higher risk of AE as two major metabolizers of bradykinin and substance P are pharmacologically inhibited.
- AE of the upper airways is a potentially lethal condition and should always be thoroughly assessed by a specialist in the field.
- Non-histaminergic AE does not respond to antiallergic medication.

The patient was carefully examined for any underlying causes of AE including allergy and complement C1-inhibitor deficiency, but no pathology was found. It is our belief that the underlying reason for the recurrent AE in this patient was interaction between the ACEI and the DPP-IV inhibitor.

Contributors TH has been responsible for and performed the writing and preparation of figures. AB has been expert cowriter. ERR had the idea to this manuscript and has been expert cowriter.

Competing interests ERR has received payment for lectures from MSD Norway and Shire. She has received research grants for HAE research from Shire and genetic studies regarding angioedema from CSL Behring and ViroPharma. AB has been involved in clinical research or educational events involving CSL Behring, Jerini, AG/Shire, Sobi, and ViroPharma. TH has participated in a conference on HAE organised and paid by Shire.

Patient consent Obtained.

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