Effective treatment of histaminergic and bradykinin related angioedema

Werner Aberer, Dept. Dermatology, University of Graz, Austria
Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- invited lectures for antihistamine-, adrenaline-, C1-INH- and Bradykinin-RA-Companies
- clinical trials with the above-mentioned drugs
- advisor and speaker for CSL Behring, Shire, and ViroPharma

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (e.g. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.
what is the diagnosis?
what is the cause?
what is the adequate treatment?

- phototoxic reaction to amiodarone
  - topical steroids; avoidance of sun, and avoidance of amiodarone
- contact allergy to p-phenylendiamine (hair-dye)
  - topical steroids, avoidance of hair dyeing
- acute attack of Hereditary Angioedema
  - iv C1-INH or s.c. icatibant
- lip swelling 1 hour after a bee sting
  - adrenaline, steroids, antihistamines, …
what is the mediator?

- a T cell-mediated process
- bradykinin
- histamine, and others
angioedema of the head/neck

a) ACE-inhibitor, angioedema tongue, intubation

b) HAE, lips

c) Sartan tx, AE lids

d) HAE larynx

mediator: bradykinin
The first steps: not to look for the relevant mediator, but find the correct diagnosis.

Laboratory Blood Tests
- C1 inhibitor concentration
- C1 inhibitor activity
- C4 and C1q

Physical Examination
- whole body
- laryngoscopy

Imaging Procedures
- ultrasound
- MRI

Medical History
- family history
- medical conditions
- past/current medications
- food, insect stings, ...

Differentiation

Responds to treatment with anti-histamines, corticosteroids, epinephrine?
- yes
- no

Presence of urticaria?
- yes
- no

Non-allergic

look for alternative treatments!

Allergic

Histamine seems to be the main mediator

allergic – non-allergic? histamine-mediated – or not?

daily life:

- look for hives → most likely histamin-mediated
- take a detailed history for allergy: food, drugs, insect stings, vaccines, etc.
- try antihistamines
- (measure mediators!?)
allergic – non-allergic? histamine-mediated – or not?

daily life at a dermatology clinic:

- urticaria +/- angioedema
  - acute, first episode

- urticaria +/- angioedema
  - chronic, periodic, intermittent,…

**manifestations:**
- urticaria alone 70%
- urticaria + AE 20%
- angioedema alone 10%

**etiology:**
- allergic 50%
- other 50%

**treatment:**
- response to antihistamines, steroids,… in most cases

**manifestations:**
- urticaria alone 80%
- urticaria + AE 10%
- angioedema alone 10%

**etiology:**
- allergic <5%
- unknown 30-70%
- other 25-65%

**treatment:**
- antihistamines OR alternatives*

* alternatives:
  - diagnosis
  - treatment
Alternative diagnoses for angioedema without urticaria

- Bradykinin-mediated diseases:
  - Hereditary angioedema
  - Acquired angioedema:
    Acquired C1-INH defect
    RAAS-inhibitor-mediated AE

- Angioedema without urticaria:
  an independent entity?
  a bundle of diseases with
  - known or
  - unknown origin
literature search in PubMed:
((angioedema) AND histamine) NOT wheals) NOT urticaria

15 results

2 “specific” papers:

- Zingale, Beltrami, Zanichelli, Maggioni, Pappalarde, Cicardi, Cicardi: Angioedema without urticaria: a large clinical survey. CMAJ 2006; 175: 1065-1070

**Related factors:** medication, food, insect bite, other allergen, other stimuli

**Unknown:**
- Responder 33% or
- Non-responder (5%) to LT-antihistamine*

**Peripheral:**
- MRS, lymph-edema, CLS, idiopathic

---

**Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, n = 776**

<table>
<thead>
<tr>
<th>Related to a specific factor*</th>
<th>Patients</th>
<th>M:F ratio</th>
<th>Age at onset, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Related to a specific factor*</td>
<td>124</td>
<td>16</td>
<td>0.51</td>
</tr>
<tr>
<td>Autoimmune disease/infection</td>
<td>55</td>
<td>7</td>
<td>0.62</td>
</tr>
<tr>
<td>ACE inhibitor-related</td>
<td>85</td>
<td>11</td>
<td>0.93</td>
</tr>
<tr>
<td>C1-inhibitor deficiency</td>
<td>197</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>183</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>14</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Unknown (idiopathic) etiology**</td>
<td>294</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Histaminergic</td>
<td>254</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Nonhistaminergic</td>
<td>40</td>
<td>1.35</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral/generalized edema***</td>
<td>21</td>
<td>3</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Note: M = male, F = female, ACE = angiotensin-converting enzyme.
*A food, drug, insect bite, environmental allergen or other physical stimulus.

**Medical University of Graz**
**Related factors:** medication, food, insect bite, other allergen, other stimuli

**Unknown:**
- 33% of all;
- Out of them 5% non-responders to LT-antihistamine*

***Peripheral:***
- MRS, lymph-edema, CLS, idiopathic

---

**Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, n = 776**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>M:F Ratio</th>
<th>Age at Onset, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to a specific factor*</td>
<td>124</td>
<td>0.51</td>
<td>39</td>
</tr>
<tr>
<td>Autoimmune disease/infection</td>
<td>55</td>
<td>0.62</td>
<td>49</td>
</tr>
<tr>
<td>ACE inhibitor-related</td>
<td>85</td>
<td>0.93</td>
<td>61</td>
</tr>
<tr>
<td>C1-inhibitor deficiency</td>
<td>197</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>183</td>
<td>0.88</td>
<td>8</td>
</tr>
<tr>
<td>Acquired</td>
<td>14</td>
<td>1.8</td>
<td>56.5</td>
</tr>
<tr>
<td>Unknown (idiopathic) etiology**</td>
<td>294</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Histaminergic</td>
<td>254</td>
<td>0.56</td>
<td>40</td>
</tr>
<tr>
<td>Nonhistaminergic</td>
<td>40</td>
<td>1.35</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral/generalized edema***</td>
<td>21</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

Note: M = male, F = female, ACE = angiotensin-converting enzyme.

*A food, drug, insect bite, environmental allergen or other physical stimulus.
“We propose an algorithm to guide clinicians in investigating cases of angioedema unaccompanied by urticaria.”

In summary:

- 16% “allergic”
- 33% idiopathic, out of them 5% non-histaminergic
- Be aware: selected population!
an approach to the patient with angioedema

Classification:
- Allergic
- Drug-related
- C1 inhibitor deficiency
- Idiopathic
- Miscellaneous cases

Consider rare cases:
- Autoimmune thyroid disease
- Connective tissue disease
- Gleich’s syndrome
- Clarkson syndrome
- NERDS

Angioedema mimics:
- Facial cellulitis
- Superior vena cava syndrome
- Thyroid eye disease
- Blepharochalasis
- Systemic amyloidosis
- Dependent oedema
- Hypoproteinemia-related e.
- Crohn’s disease
- Eosinophilic fasciitis
- Acute idiopathic scrotal e.
- Burns
- Infections (viral, parasite)

Grigoradou / Longhurst, Clin Exp Immunol 2012
In summary: we need an individual approach!

- After a bee sting: This patient responds to **antihistamines** well.

- After hair dyeing: This patient responds to **steroids**.

- And this patient does NOT respond to antihistamines or steroids, because she suffers from **HAE**.
Diagnostic Algorithm for AE with C1-INH deficiency

Clinical symptoms:
- recurrent angioedema without urticaria
- recurrent episodes of abdominal pain & vomiting
- laryngeal oedema
- positive family history

Laboratory measures:
- C4 levels
- C1-INH antigenic protein
- C1q levels

C4; C1-INH; C1q all normal
Determine:
- C1-INH function
- repeat C4 levels (during attack)
  all normal (even during attack)
Consider other forms of angioedema
- HAE type III
- ACEi-AE
- IAE

C4 low
C1-INH; C1q normal
Determine:
- C1-INH function
  C1-INH function low

Diagnosis: HAE-I
confirm with 2nd measure of C4, C1-INH levels and function

C4; C1-INH low
C1q normal
Determine:
- C1-INH function
  C1-INH function normal

Diagnosis: HAE-II
confirm with 2nd measure of C4, C1-INH levels and function

C4; C1q low
C1-INH normal/low
Determine:
- C1-INH function
  C1-INH function low

Diagnostic Algorithm for AE with C1-INH deficiency
HAE-treatment options 2016

Selecting an appropriate treatment

- **Frequent attacks or severe attacks**
  - Long-term prophylaxis
  - Attenuated androgens ?
  - Antifibrinolytics
  - **C1-INH concentrate**

- **Dental procedure, surgery, trauma, delivery, vacation in foreign country**
  - Short-term prophylaxis
  - **C1-INH concentrate**
  - Attenuated androgens
  - Antifibrinolytics

- **Life-threatening, moderate to severe attacks**
  - Acute treatment
  - **C1-INH concentrate**
  - Receptor-antagonists
  - Bradykinin-R-blocker
  - Kallikrein-Inhibitor
TREATMENT

- All patients diagnosed with HAE due to C1-INH deficiency should have available at home two doses for treating an acute attack:
  - C1-INH (pd 3000 units, rh 4400 units)
  - or
  - Ecallantide (60 mg)
  - or
  - Icatibant (60 mg)
- Patients should be trained for self administration
- All attacks should be treated as soon as they are recognized
- Any of the above drug can be used for any location
- Any location can be treated at home
- Hospital recommended when risk of laryngeal involvement persist after initial treatment
Gynecologic and obstetric management of female HAE-patients:

- **Topics:** Contraception, pregnancy, parturition, breast cancer and androgens/antiestrogens, genetic counseling, infertility, abortion, lactation, menopause treatment, endometrial cancer, attack treatment
- Caballero T et al. JACI 2012; 129: 308-320

Children and adolescents with HAE – therapeutic strategies:

- **Topics:** Diagnosis as early as possible; treatment: plasma-derived C1-INH currently best option, for attack and prophylaxis

Recent guidelines with focus on self-administration of therapy:

- **Main message:** self-administration of therapy resolves attacks quickly, safely and minimises burden of disease; but there are still many barriers
- Cicardi M et al. Int Arch Allergy Immunol 2013; 161: Suppl 1: 3-9
A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

Murat Baş, M.D., Jens Greve, M.D., Klaus Stelter, M.D., Miriam Havel, M.D., Ulrich Strassen, M.D., Nicole Rotter, M.D., Johannes Veit, M.D., Beate Schossow, Alexander Hapfelmeier, Ph.D., Victoria Kehl, Ph.D., Georg Kojda, Pharm.D., Ph.D., and Thomas K. Hoffmann, M.D.

ABSTRACT

BACKGROUND
Angioedema induced by treatment with angiotensin-converting–enzyme (ACE) inhibitors accounts for one third of angioedema cases in the emergency room; it is usually manifested in the upper airway and the head and neck region. There is no approved treatment for this potentially life-threatening condition.

METHODS

Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema.
Greve J1, Bas M2, Hoffmann TK1, Schuler PJ1, Weller P3, Kojda G4, Strassen U2.

Abstract
OBJECTIONS/HYPOTHESIS: The study objective was to generate pilot data to evaluate the effectiveness and safety of C1-esterase-inhibitor concentrate (C1-INH) compared to standard treatment in patients with angiotensin-converting enzyme inhibitor (ACEi)-induced angioedema affecting the upper aerodigestive tract.

STUDY DESIGN: Proof-of-concept case series with historical control.

METHODS: Adult patients with angioedema in the upper aerodigestive tract presenting to the emergency department were included. After establishing the diagnosis of ACEi-induced angioedema based on patient history and thorough clinical examination, all patients were administered 1,000 international units (IU) of C1-INH intravenously. A historical control group consisting of adult patients with ACEi-induced angioedema who had been treated with intravenous corticosteroids and antihistamines at the same institution over the past 8 years was used for comparison. The most important parameters assessed were the time to complete resolution of symptoms and the need for intubation or tracheotomy.

RESULTS: Ten patients were included in the C1-INH group and 47 in the corticosteroid/antihistamine group. The time to complete resolution of symptoms was considerably longer in the historical control group (33.1 ± 19.4 hours) than in the C1-INH group (10.1 ± 3.0 hours). No intubation or tracheotomy was needed in the C1-INH group (0/10 patients), whereas three out of the 47 historical controls required tracheotomy and two were intubated (5/47).

CONCLUSION: The results suggest a role for C1-INH as an effective and safe therapeutic option in patients with ACEi-induced angioedema, which needs to be confirmed by further larger and double-blinded studies.

LEVEL OF EVIDENCE: 4.
Effective treatment of histaminergic and bradykinin related angioedema

First: make a correct **diagnosis**, Then: find the best **treatment**!