Angioedema

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Disclosure

• Advisory board viropharma
Angioedema

- self-limited
- localized subcutaneous (or submucosal) swelling
- which results from extravasation of fluid into interstitial tissues.
• in isolation
• accompanied by urticaria
• as a component of anaphylaxis.
It is not only the face
Epidemiology

- US: 80,000 – 112,000 ED/annually
- 18% of ED for angioedema results in hospital admission
- Hospitalization rate: 4:100,000 persons

- Lifetime prevalence 7.4%
- Underlying cause identified in 20-40%
• Mast cell driven
• Bradykinin
• unknown
Pathophysiology: Mast cell induced angioedema
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- IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNF, MIPs, IFN-γ, GM-CSF, TGF-β, bFGF, VPF/VEGF, PGD₂, LTB₄, LTC₄, PAF, histamine, serotonin, heparin, chondroitin-sulfate, chymase, tryptase, CPA

- Activation → PRURITUS

- Vasodilation → ERYTHEMA

- Extravasation → WHEAL

- Recruitment → INFILTRATE
Pathophysiology: bradykinin induced angioedema
Pathophysiology: bradykinin induced angioedema

- Inhibition of bradykinin degradation
- Increased bradykinin production
Pathophysiology: bradykinin induced angioedema

Hageman factor
Trypsin
Kallikrein

Plasma
prekallikrein

Plasma kallikrein

HMW kininogen → Bradykinin

Aminopeptidases

LMW kininogen → Kallidin

Tissue kallikreins

Kininases I and II

Inactive fragments
Pathophysiology: bradykinin induced angioedema

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Kininases I and II

Inactive fragments

ACE inhibitors
ACE inhibitor induced angioedema

- Prevalence 0.1-2.2%
- About 1/3 of angioedema cases on the ER
- 50% within one week of start treatment
- Relatively often involvement gastro-intestinal tract
Increased bradykinin production

Figure 1. How C1 inhibitor regulates bradykinin production

- Contact activation XIIa
- C1INH
- Fibrinolytics (TXA eACA)
- Kallikrein
- KMWK
- Bradykinin
- Ecallantide
- Icatibant
- Increased vascular permeability and inflammation
- MAC
- C3a
- C5a
- Cell injury
Pathophysiology: bradykinin induced angioedema

A. Complement
- C1r
- C1s
- MASP2
- C4-C2

B. Coagulation fibroanalysis
- t-PA
- FXIIa
- Plasmin
- FXIa
- FIxa
- FDP
- FXa

C. Kinin contact
- FXIIa
- Kallikrein
- HMWK
- Bradykinin

D. FXIIa-Kallikrein
- HMWK
- CK-1
- uPAR
- gC1q-R

E. Bradykinin
- BK2-R
- Oedema
- Plasma leakage
- Oedema
- Oedema
- Oedema
- Oedema
- Oedema
- Oedema
Pathophysiology bradykinin induced angioedema
HAE

• Three types
  – Type I: low concentration of C1-inh
    • Inherited
    • aquired
  – Type II: functionally abnormal C1-inh
  – Type III: estrogen dependent
    • 20% mutation in FXII
HAE

• Prevalence: 1-50 / 100.000 persons
• Median attack frequency: 1 / 45 dagen
• Annual cost per patient (without treatment): 42.000 – 92.000 $
HAE

- Increased attack risk
  - Physical and emotional stress
  - ACE inhibitor use
  - Exposure to estrogens
Why and how to make a difference

• Why?
  – Different treatment approach
  – Different approach in prevention

• How
  – By careful anamnesis
  – By looking at the skin
  – Sometimes by laboratory analysis
Urticaria
Urticaria pigmentosa
Erythema marginatum
What laboratory analyses should be performed

- Tryptase
- C4
- (C1-inhibitor)
  - Concentration
  - Activity
Differential diagnosis

- Peri-orbital contact dermatitis
- Infection (cellulitis)
- Auto-immune disease
- Superior vena cave syndrome
Differential diagnosis

Treatment angioedema

• In general
  – Focus on vital signs
  – Examination of the airways, skin and abdominal regions
  – Consider flexible fiberoptic laryngoscopy

Fig. 1. Patient with mild, nonobstructive, supraglottic edema secondary to angiotensin-converting enzyme inhibitors who was observed in the intensive care unit and had no significant progression on serial examinations.
Treatment: mast cell mediated

• Life threatening:
  – Secure airway
  – Epinephrine + actions taken below
• Not life-threatening
  – H1-receptor antagonist
  – H2 receptor antagonist
  – Corticosteroids

• Usually relatively quick response
Treatment bradykinin associated angioedema

• Life threatening
  – C1-inhibitor
    • Plasma derived
    • Conestat alfa (recombinant C1-esterase inhibitor)
  – Icatibant (bradykininereceptor type 2 antagonist)
  – Ecallantide (plasma kallikreine inhibitor)
  – FFP
  – (epinephrine)
  – Corticosteroid / H1-receptor blockers?

• Not life-threatening
  – Wait and see
  – Consider prophylactic treatment
Primary Outcome in the Trial of C1 Inhibitor Therapy for Acute Attacks of Angioedema.

Cost of treatment

• Plasma derived C1-inhibitor
  – Per 500 IE: € 770
  – Usually 1000 IE per attack
  – Median attack frequency: 8 / year

  – Total cost: > €12,000
Treatment in ACE inhibitor induced angioedema

TOXICOLOGY/BRIEF RESEARCH REPORT

Therapeutic Efficacy of Icatibant in Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: A Case Series

Murat Bas, MD, Jens Greve, MD, Klaus Stelter, MD, Henning Bier, MD, Thomas Stark, MD, Thomas K. Hoffmann, MD, Georg Kojda, PharmD, PhD

From Hals-, Nasen- und Ohrenklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany (Bas, Bier, Stark); the Department of Otorhinolaryngology, University of Essen, Essen, Germany (Greve, Hoffmann); the Department of Otorhinolaryngology, University of Munich, Munich, Germany (Stelter); and the Institute of Pharmacology and Clinical Pharmacology, University of Duesseldorf, Dusseldorf, Germany (Kojda).
Mean time (hours) until complete resolution of symptoms in the 8 patients treated with icatibant and in a historical group of patients receiving standard therapy with methylprednisolone and clemastine.
Prophylaxis

• When to give prophylaxis

<table>
<thead>
<tr>
<th>Consideration criteria</th>
<th>Prophylactic therapy</th>
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<tbody>
<tr>
<td>Frequency of attacks</td>
<td>≥1/month</td>
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<tr>
<td>Rapid progression of attacks</td>
<td>Yes</td>
</tr>
<tr>
<td>Timely access to care</td>
<td>No</td>
</tr>
<tr>
<td>History of laryngeal attacks</td>
<td>Yes</td>
</tr>
<tr>
<td>Emergency visit to physician/hospital</td>
<td>&gt;3/year</td>
</tr>
<tr>
<td>Intubation due to HAE</td>
<td>Yes</td>
</tr>
<tr>
<td>Hospitalized due to HAE</td>
<td>&gt;1/year</td>
</tr>
<tr>
<td>ICU due to HAE</td>
<td>Yes</td>
</tr>
<tr>
<td>Missed days of school or work</td>
<td>≥10–15 days/year</td>
</tr>
<tr>
<td>Impacts lifestyle (vacation, family, sports)</td>
<td>Yes</td>
</tr>
<tr>
<td>Analgesic dependency</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Notes:** These therapy consideration criteria are for guidance only. Therapy decisions are always based on close consultation between physician and patient on what the best course of therapy should be for a patient's particular needs, problems and concerns. Adapted from Craig et al.11

**Abbreviation:** HAE, hereditary angioedema.
Prophylaxis

• Androgens
  – Danazol (max 200 mg/day)
  – Stanazol (2 mg/day)
• Cyklokapron (max 4,5 g/day)
• C1-inhibitor