Allegheny Health Network

Angioedema: Diagnosis & Management

Christine Rauscher, MD

11/1/24

Disclosures

Speakers bureau: AstraZeneca

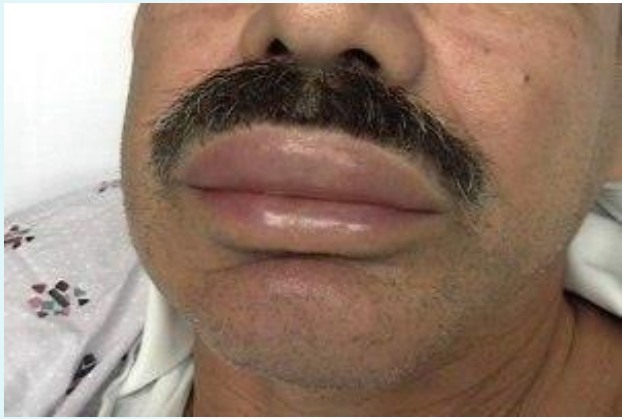
Objectives

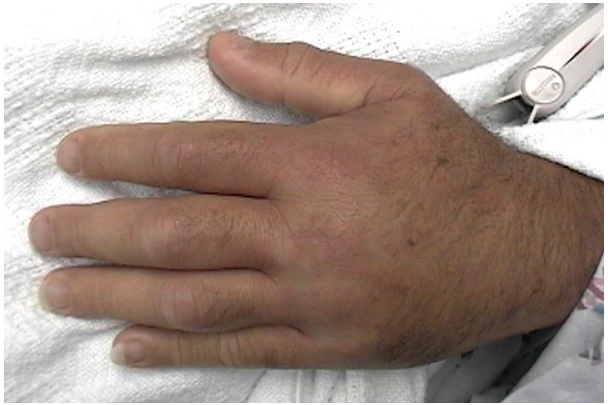
- Review clinical characteristics & differential diagnosis of Angioedema
- Discuss management options for patients with Angioedema

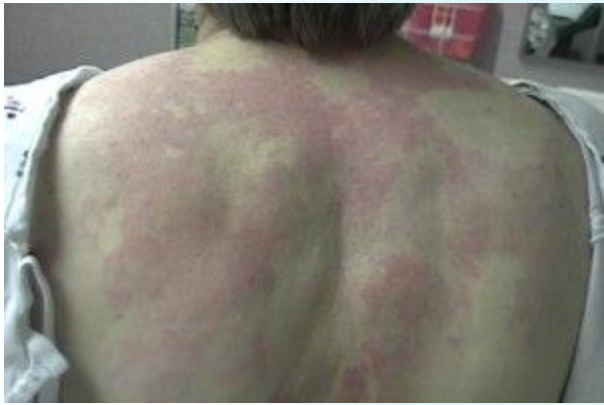
Angioedema: Definition

- Rapid swelling below the surface of the skin
- Self-limited & localized
  - Ie not constant swelling (ie macroglossia)
- Results from extravasation of fluid into interstitial tissues or fluid buildup
- Usually asymmetric & non-pitting
  - Usually not gravity dependent

Angioedema







But are there any hives?

Histaminergic vs Bradykinin Angioedema

	Histamine	Bradykinin
Urticaria	Common	Rare
Severity of swelling	Lesser	Greater
Duration of swelling	Shorter	Longer
Risk for fatal airway obstruction	Exceedingly low	Appreciable
Abdominal Attacks	Rare	Very common
Response to antihistamines, corticosteroids, epinephrine	Excellent	Poor

Management of histaminergic Angioedema (ie typically with urticaria)

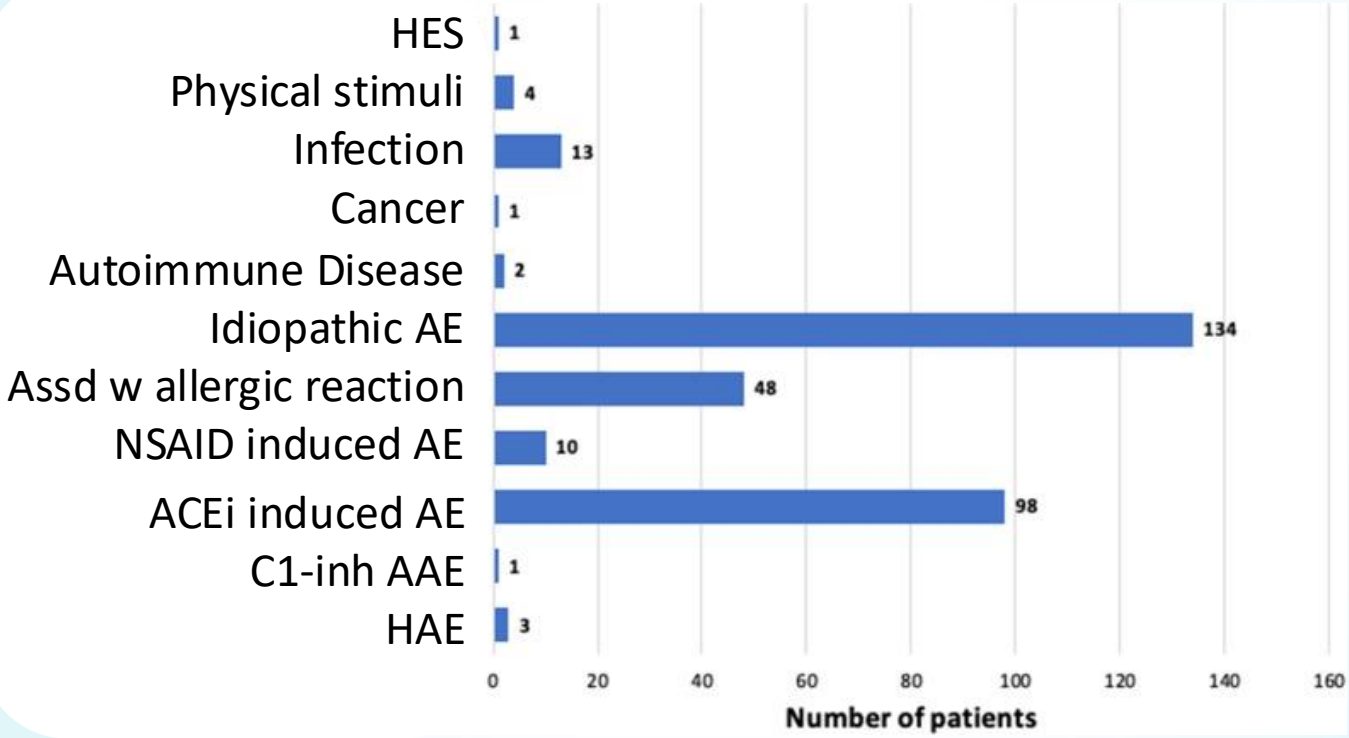
- Consider oral steroids
- Consider scheduled non-sedating antihistamines
  - Up to 4 tabs/day
- If 6 weeks or longer consider omalizumab (anti-IgE therapy)

Clinical Characteristics of Angioedema Patients in a Tertiary Care Hospital

- Retrospective cohort
  - 1996-2014
- 315 patients identified
  - Excluded if urticaria

Pall et al. J Asthma Allergy. 2020.

Underlying Factors Among Angioedema Patients (n=315)



Pall et al. J Asthma Allergy. 2020.

Angioedema without urticaria: a large clinical survey

- Tertiary level center where patients referred mostly by specialists
- Reviewed all patients with angioedema w/o urticaria
  - 1993 - 2003
- Identified 929 pts & 776 pts completed “full work-up”

Angioedema without urticaria: a large clinical survey

- Clinical history and physical exam
- CBC, SPEP, CRP, ESR, LFTs, TSH, ANA
- C4, C1 inh level & function, C1q
- Stool studies, U/A
- Sinus & dental x-rays

If evaluation was negative, antihistamine treatment for 1 month was initiated

Angioedema without urticaria: Classification of 776 pts

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

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Zingale CMAJ 2006

Angioedema without urticaria: Causative agent identified subset (n=124)

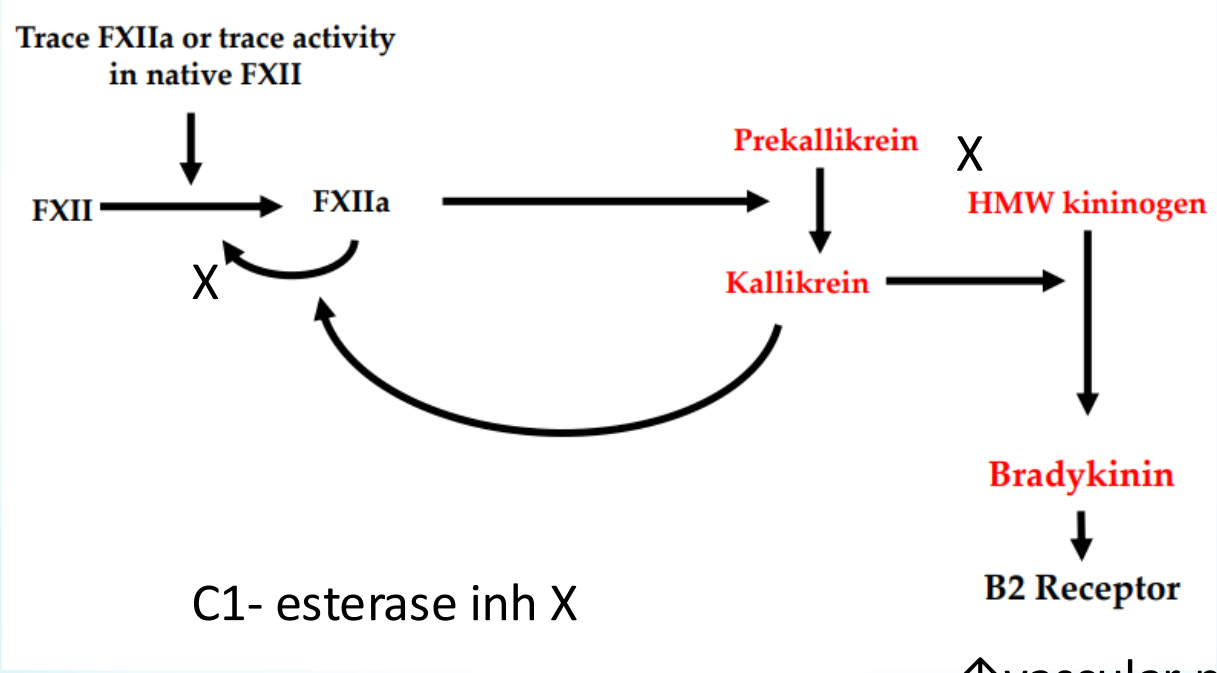
Recurrence of symptoms was clearly related to an exogenous stimulus with a consistent cause-effect relationship

- Medications (N=56)
- Food (N=45)
- Medication & Food (N=10)
- Insect bite (N=5)
- Environmental allergen (N=4)
- Physical irritation/stimulus (N=4)

Bradykinin angioedema

Hereditary

- Rare, potentially life-threatening
- Prevalence is 1:10,000 to 1:150,000
- HAE with C1inh deficiency is autosomal dominant
- Family history is key but 25% of mutations are de novo



C1- esterase inh X

↑vascular permeability

Complement testing in Recurrent Angioedema

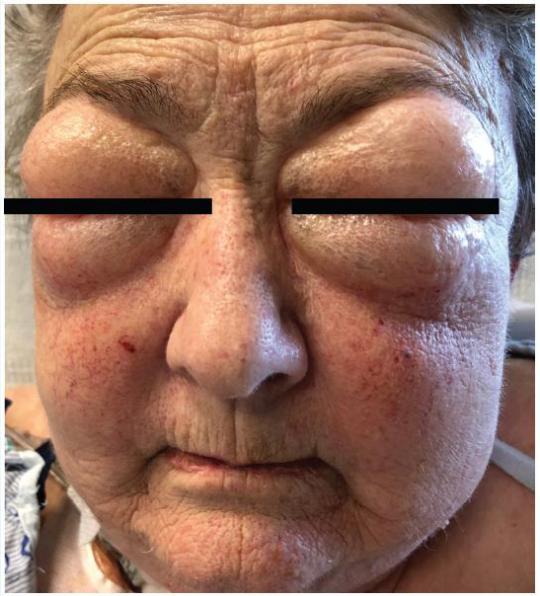
Type	C1-inh level	C1-inh function	C4 level	C1q level
HAE Type I	↓	↓	↓	Normal
HAE Type II	Normal / ↑	↓	↓	Normal
HAE with normal C1-inh	Normal	Normal	Normal	Normal
Acquired C1 inh	↓	↓	↓	↓
ACE-I assd AE	Normal	Normal	Normal	Normal
Idiopathic AE	Normal	Normal	Normal	Normal

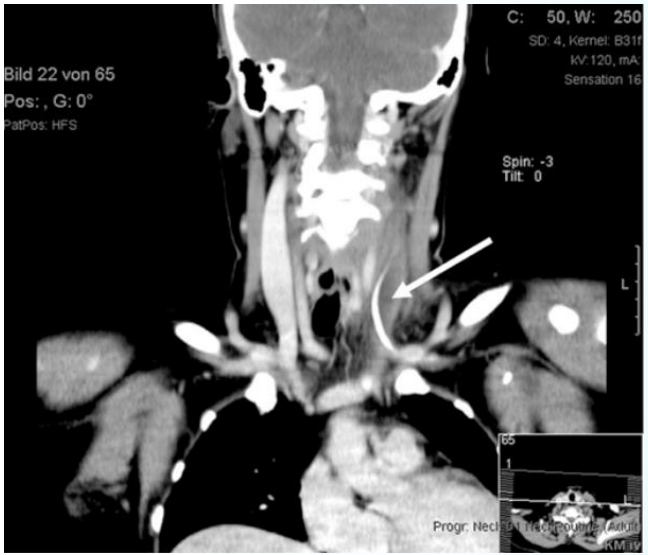
Management of Acute HAE Attacks

	Mechanism	Population	Notes/Adverse reactions
Icatibant (Firzayr)	Bradykinin B2 receptor antagonist	U.S. approved age ≥ 18y, Europe ≥ 2y	- SC - Injection site discomfort
C1inh concentrate Plasma-derived (Berinert, Cinryze)	Inhibits kallikrein, factor XII, other factors	U.S. & Europe approved for children & adults	- IV - Possible infection
Recombinant human C1INH (Ruconest)	Inhibits kallikrein, factor XII, other factors	U.S. & Europe approved ≥ 12 y	- IV - Rare anaphylaxis in rabbit-sensitized people
Ecallantide (Kalbitor)	Inhibits kallikrein	U.S. approved ≥ 12 y	- SC - Risk of anaphylaxis (2%)/Administered by HCP

Plasma considered second line therapy

What mimics angioedema?





West et al. Allergy Asthma Proc. 2020.
Image credit: https://www.researchgate.net/figure/CT-scan-representing-thrombosis-of-the-left-internal-jugular-vein-due-to-a-dislocated_fig1_38012445

Angioedema Take Home Points

- Angioedema without urticaria should raise suspicion for bradykinin-mediated angioedema
  - Bradykinin-mediated angioedema: ACEI, HAE-C1INH, HAE-nl-C1INH, C1INH-AAE
- Diagnosis requires clinical assessment, and if appropriate: C4, C1 inhibitor level & function
  - if C1INH-AAE is suspected – C1q
- HAE management consists of: accessible on-demand treatment for acute attacks for all patients, and when indicated – prophylactic therapies
- Antihistamines, epinephrine & corticosteroids are not effective for bradykinin-mediated angioedema

Questions?