Hereditary angioedema: past, present and future

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Objectives of talk

• “A positive future with HAE”

• Historical overview
• The current state of play
• Where the future might go

• “Study the past if you would define the future” Confucius
The past

• Earliest description of angioedema 1586
  – Marcelo Donati – reported a young count who had lip swelling and sensitivity to eggs
• More detailed descriptions in the medical literature from the late 1800s
• John Laws Milton in 1876 described “giant urticaria”
• Heinrich Quincke in 1882, described acute circumscribed oedema
  – “Quincke’s oedema”
  – “Angio-neurotic oedema”
The past

Genius at Work: Osler’s 1888 Article on Hereditary Angioedema

Richard D. deShazo, MD and Michael M. Frank, MD


In the minds of many, William Osler remains our greatest physician (Figure 1). At a time when little was known about modern physiology, he had the unprecedented ability to analyze disease symptoms and place them in a pathophysiologic context. His article on hereditary angioneurotic edema, as it is titled, is an example of his genius.

Although the familial nature was not documented in that patient, Osler’s report was much more detailed than any previous report on the disease.

In the discussion of his article, Osler noted that he had seen another patient with the hereditary angioneurotic edema and compared and contrasted the clinical findings in the family of Mrs. H and that patient with reports from 14 other authors. These included the reports of Riehl, Matas, Henoch, and Quincke, the latter of whom named the condition. He questioned Quincke’s name of the condition and opinion as to its

- William Osler in 1888
  - Described an inherited form of angioedema
  - “Hereditary angio-neurotic oedema”
    - Neurotic has since been dropped from the label
      - Neurosis not part of the cause of the swelling
HEREDITARY ANGIO-NEUROTIC OEDEMA

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AND TO THE INFIRMARY FOR NERVOUS DISEASES.

UNDER the terms acute local, acute circum-
scribed or angio-neurotic oedema, a disease has been
described, characterized by the sudden onset in var-
ious regions of oedematous swellings, more or less
limited in extent, and of transient duration. Al-
though not referred to at any length in text-books or
cyclopaedias, the affection is evidently not very un-
common, as Dinkelaker,
1 a pupil of Quincke, has
collected a number of cases from the literature.
Quincke has himself referred to the subject in
Monatshefte für praktische Dermatologie, 1888.
Jameson,
2 of Edinburgh, has written on the subject
and Graham,
3 has given a good account of the dis-
ease. Riehl,
4 Falcone,
5 Strübing,
6 Matas,
7 have re-
cently reported cases.

In three instances the disease appeared in
succeeding generations, and it is this hereditary
aspect which gives special interest to the following
report.

Briefly summarized, the affection in the family
which I have studied has the following characteris-
tics:

1. The occurrence of local swellings in various parts of the
   body, face, hands, arms, legs, buttocks, and throat.
   In one instance, possibly in two, death resulted from a sudden
   Oedema glutidum.
2. Associated with the Oedema, there is almost invariably gas-
   tro-intestinal disturbance: colic, nausea, vomiting, and some-
   times diarrhoea.
3. A strongly marked hereditary disposition, the disease having
   affected members of the family in five generations.

A member of the family, Mrs. H., aged twenty-
four years, was admitted to the Infirmary for Nervous
Diseases, September 20, 1887, and the following notes
were taken by Dr. Burr, the house physician:

Medium sized, well-nourished brunette, admit-
ted with neuroasthenic symptoms. Has been married
two years, no children. Has had good deal of back
pain and menstruation is irregular and painful; was
healthy as a child, and as a young woman. As long as
she can remember, she has been subject to attacks of
transient swelling in various parts—hands or fin-
gers, knee caps, elbows, buttocks, arm or thigh in
flabby parts, face, or more often the lips alone. The
fingers have been so swollen that it was impossible
to move them, and once the ring-finger was so
greatly enlarged that the ring had to be filed off to
prevent gangrene. The underslip has been swollen to
such a degree that the mouth could not be opened,
and milk had to be poured in from above. A slight
redness and itching of the part is first noticed, or
a sensation of heat; the redness is not always present.
The effusion may take place with great rapidity. She
often has red spots on various parts of the skin, or
irregular lines of redness without any swelling. The
duration varies from one to four days. There is not
much itching, particularly when the swelling is
great, but a sense of distention and stiffness. When
fully out it does not pit, but does so when going
down. The attacks may come on when she is feeling
quite well or there may be slight indisposition. In all
the severer ones there is abdominal pain, described
as colic, with nausea, and often vomiting. There is
sometimes headache; no fever. The attacks have no
relation to the menstrual flow. She rarely passes
two weeks without an attack. She does not think that
food has any influence on her case. She remained in
the hospital three weeks, during which time there
was no severe attack, but she had numerous wheal-
like eruptions on the chest and sides of the thighs,
with very slight swelling, and the day before she left
there was a large spot of local oedema on the inner
aspect of the left thigh. Dr. Morton dilated a very
narrow cervix, and she went home much improved.
She had not passed three weeks without a severe
attack for a long time. I saw her again on January
18th. She had four or five bad attacks on the hands,
feet, and thighs, since leaving the hospital.
The past

• William Osler in 1888
  – Mrs H
  – 24 year old
  – Admitted to the Infirmary for Nervous Diseases
  – “Transient swellings in various parts”, “colic”
  – 5 generations of affected family members
  – 2 family members had died of the disease
• Mentioned that angioedema had been described by others at the time
• Impressively accurate description
  – No google/internet/etc but aware of the work of other doctors at the time
The past

• 1917 – Crowder and Crowder describe HAE as an autosomal dominant trait i.e. children have a 50% chance of inheriting the condition from an affected parent, regardless of gender
• 1961 – Lepow discovered a naturally occurring inhibitor of C1 esterase
  – Showed that C1 esterase made vessels more leaky in guinea pig skin, and this could be prevented with C1 inhibitor
• 1962 – Landerman described a patient with HAE who had reduced amounts of an inhibitor of kallikrein, and that suggested that kallikrein could start the formation of oedema
The past

• 1963 – Donaldson and Evans described 3 families with no detectable C1 inhibitor levels
  – Unaffected relatives had normal levels
• 1986 – Davis - C1 inhibitor gene (SERPING1) localised to chromosome 11
• 1998 – Bradykinin proposed as a main mediator of angioedema
• 2000 – HAE with normal C1 inhibitor described
  – 2006 – mutation in Factor XII identified in Germany
  – 2017 – angiopoietin-1 mutation identified in Italy
  – 2018 – plasminogen mutation identified in Germany
A timeline of treatments

• 1960 - Spaulding tried methyltestosterone
• 1969 – Use of fresh frozen plasma reported, risk that this can make swelling worse
• 1972 – EACA/tranexamic acid tried, reports by 3 different groups
• Late 1970s – investigators use C1 inhibitor concentrate
A timeline of treatments

• Berinert – licensed in Europe from 1979 onwards for acute treatment
  – Only approved by FDA in USA in 2009 (acute attacks)
  – Registration trial 2007

• Cinryze
  – Trial in prophylaxis (prevention) done
  – Licensed in USA 2008 (prophylaxis) , licensed in EU 2011

• Ecallantide – kallikrein inhibitor – approved in USA in December 2009 for acute treatment
  – Not approved in Europe
A timeline of treatments

- **Ruconest** (recombinant C1 inhibitor)
  - Made from breast milk of transgenic rabbits
  - Not derived from human plasma
  - Licensed in EU 2010, licensed in USA 2014

- **Icatibant** (bradykinin antagonist)
  - Licensed in EU 2008, licensed in USA 2011
  - Subcutaneous administration
  - Improves ease of self-administration for acute treatment
    - In general, treatment more effective if used sooner
A timeline of treatments

• More recently
  – Haegarda – subcut plasma-derived C1 inhibitor for prophylaxis – approved in USA
  – Lanadelumab – subcut monoclonal antibody against kallikrein – approved in USA

• Ruconest for prophylactic/preventative – phase II trial completed

• BCX7353 – oral kallikrein inhibitor – ongoing phase III trials
A timeline of treatments

• Things in earlier development
  – CSL312 (subcut) – monoclonal antibody which inhibits factor XIIa
  – Ionis ASO (antisense oligonucleotide) – prekallikrein antisense knockdown (subcut)
  – Adverum ANN-002 – adeno-associated virus, gene therapy ? On hold (subcut)
  – Kalvista – oral kallikrein inhibitor, KVD900 due to enter phase 2 clinical trials for on-demand treatment
The present

• A lot has changed in the last 10 years!
  – Despite the slow timeline before

• Scientific understanding of disease is now well worked out
• This allows targeted development of new medication

• In addition to better therapies, this is also more focus on:
  – Quality of life/burden of illness issues
  – Psychological issues
  – Organisation of care
Guidelines... have proliferated

- Good as they allow better standardisation of care to the best practice
  - 2003 – Canadian
  - 2005 – UK consensus
  - 2007 – Canadian Hungarian
  - 2010 – Canadian-American-European
  - 2010 – Home therapy guidelines
  - 2011 – HAWK (Hereditary Angioedema International Working Group)
  - 2011 – Paediatric guidelines
  - 2012 – WAO (World Allergy Organisation)
  - 2012 – Obstetric/gynaecology guidelines
  - 2013 – US practice parameter
  - 2014 – Canadian guidelines
  - 2014 – UK consensus revision
  - 2017 – WAO/EAACI (European Academy for Allergy and Clinical Immunology) revision

- And others...
And in the UK

• Commissioning policies in England
  – April 2013 – acute attacks in HAE
    • C1 inhibitor and icatibant
  – July 2016 – C1 inhibitor for prophylaxis/prevention
    • 2 or more attacks on oral prophylaxis(prevention) for at least 8 weeks
      – Definition of clinically significant attacks – either affecting head and neck areas, or disabling
    • Or oral treatment is not suitable/contraindicated e.g. pregnancy

•
The present

• Evolution of treatment
  – Increased move towards self-administration
    • Improves speed of access to treatment – increases effectiveness
    • Also remove some of the need for attendance at A&E departments
  – Change in approach towards treating attacks
    • Treatment of disabling /peripheral attacks as there is an understanding of the morbidity/time lost from work/school/etc
    • Burden of illness studies

• Psychological effects of the illness

• HAE registries started
  – Better pooling of data to understand a rare condition
The future

• “The past was always there, lived inside of you, and it helped to make you who you were. But it had to be placed in perspective. The past could not dominate the future.” Barbara Taylor Bradford

• “Change is the law of life. And those who look only to the past or present are certain to miss the future” John F. Kennedy
The future

• Exciting times ahead
  – Lots of new medications in the pipeline
  – Greater focus on HAE with attention being paid to other aspects of the disease

• Challenges
  – Access to medications
  – Inequitable access worldwide
    • Will new medications be available in the UK?
  – Where will these medications fit in the way HAE is treated?
  – “Why does a patient need to wait until they become unwell before having treatment?”
    • Will we get to the stage where we generally aim to stop attacks from happening rather than treating after they have started?
Conclusions

- HAE was first described 130 years ago
- There has been relatively little progress until the last decade where things have greatly accelerated

- The trajectory and rate of progress has been very rapid in the last decade
- We have come a long way since 1888 and the future is positive
Questions?