THE NORTHERN HOSPITAL

HEREDITARY ANGIOEDEMA

Astronomer Knud Jahnke points out the planet Venus on a projection screen, as it transits the Sun on 8th June 2004, (Einstein Tower Potsdam, Germany).

"I recommend it therefore again and again to those curious astronomers who, when I am dead, will have an opportunity of observing these things, that they remember my admonition, and diligently apply themselves with all imaginable success; in the first place, that they may not by the unreasonable obscurity of a cloudy sky be deprived of this most desirable sight, and then, that having ascertained with more exactness the magnitudes of the planetary orbits, it may redound to their immortal glory".

Edmond Halley, 1716

In 1627, largely by virtue of his masterful analysis of the astronomical tables of the observations of Tycho Brahe, Johannes Kepler was able to predict a rare astronomical event - the transit of Venus across the face of the Sun, as seen from the Earth. He predicted that this event would occur in the years 1631 and again in 1761. Unfortunately he was never destined to be able to confirm his prediction for two reasons - firstly he was unable to ascertain exactly where on the surface of the Earth this event could be witnessed from and secondly he died in 1630. Then just 8 years later a brilliant self educated amateur English astronomer, at the age of just 20 years, by the name of Jeremiah Horrocks, who had been poring over Kepler's figures, suddenly realized that the great man had failed to see that the transits occurred in pairs, eight years apart, within a recurring 243 year cycle. This cycle consisted of transits at intervals of 8, 105.5, 8 and 121.5 years repeated over and over. This meant that the next transit was due in just one month's time - the next opportunity would not come for another 121.5 years! He hurriedly set up a makeshift apparatus using a simple lens refractor focused onto a large white card to view the event. On the predicted day he was frustratingly called away on Church business at around 1.00 pm. When this was finished he frantically rushed back to his house and on his return at 3.15 pm discovered the transit in progress, just as he had predicted. A small black dot was seen superimposed on the image of the Sun, passing slowly across its face. His careful observations allowed him to make a rough estimate of the size of the planet - the first scientifically based estimate of the size of another world. Tragically Horrocks died of an unknown cause shortly after his astonishing observations, and the world lost a most promising astronomer. Today Jeremiah Horrocks is largely, and most unjustly forgotten.

Seventy seven years after Horrocks' death, in 1716, the great Edmond Halley, (of Halley's Comet fame), intrigued by the young astronomer's work, and having put a great deal of study into it, published an urgent appeal to the astronomers of the future. By painstaking study he realized that if the phenomenon were observed simultaneously at multiple widely separated places on the Earth, by elegant trigonometric calculations, an accurate measure of the distance of the Earth from the Sun could be made. This had profound implications, because at the time all the ***relative*** *distances of the planets from the Sun were known - but the* ***absolute*** *distances remained completely unknown. By knowing just one value, in this case the distance of the Earth to the Sun, (today known as the "Astronomical Unit"), all other planetary distances from the Sun could be deduced. At stake was the knowledge that for the first time in history the true scale of the (then known) Solar System would be known. Humanity would make a great advance in its understanding of its place in the Universe. But by the time of the next transit, in 1761, Halley knew of course that he would be long dead - he would never know the true scale of the heavens, which so fascinated him. And so he published an impassioned plea to the astronomers of the future - those of the year 1761 not to let the opportunity pass them by - but instead, to solve one of science's greatest mysteries, which would bring to those future discoverers "immortal fame and glory".*

Halley's challenge electrified the scientific community, and over the ensuing two generations great plans of epic seagoing voyages to the most far reaching and exotic lands on the planet were laid. Great ships would carry the very latest, cutting edge, scientific instruments to make the necessary precision measurements to achieve Halley's noble quest, instruments that would include John Harrison's seagoing chronometer that

could for the first time accurately measure the hitherto elusive but critical longitude. Halley's impassioned appeal, had essentially launched what amounted to an international space race of the 18th and 19th Centuries. British, French, German and American scientists would vie for the honour of "immortal fame and glory". With one of great secrets of nature so tantalizingly close to humanity's grasp, astronomers did something unprecedented. So important a holy grail as the size of the "universe" inspired a decision of international cooperation. The great European powers such as Britain and France held colonies all over the world, so astronomers were motivated to organize the first truly international scientific project in human history. While the scientists held this noble position in the pursuit of human knowledge, the politicians of the time unfortunately held quite different ideals. The year 1761, happed to coincide with a titanic struggle between Great Britain and France for global colonial domination in a bitter conflict now known to history as the Seven Years War (1756-1763), a conflict that Churchill once labeled as the true "First World War". Although fought principally in North America (where Britain, the eventual victors, would gain Canada from France) in India and to lesser extent in Europe, the conflict also raged between the Royal Navy and the French Navy on the high seas. It need hardly be said that conflict on the high seas between the superpowers of the day did not provide a congenial milieu for scientific cooperation between the combatants! Many expeditions ended in disappointment and disaster, most spectacularly of all that of the astronomer Charles Mason and the surveyor Jeremiah Dixon, (the two who would later become famous for marking the boundary between Pennsylvania and Maryland - the Mason-Dixon line that marked the American Civil War boundary between the North and the South). Their expedition to Sumatra to measure the transit was mercilessly cut to pieces when they encountered a French frigate.

The Seven Years War ended in 1763 and the opportunity to fulfill Halley's dream in 1761 had been only a partial success. One last chance remained however, the transit of June 3, 1769. This would be the last opportunity to make the crucial measurements for another 105 years. This time there would be no mistakes. The pivotal mission was entrusted to a then little known, Yorkshire born naval captain who all the admiralty nevertheless agreed was probably the most brilliant navigator Britain had ever produced, a certain James Cook. Cook sailed without incident to the remote island of Tahiti in the Southern Pacific Ocean, and there from a sunny hilltop made the vital measurements of the transit of Venus. Upon his return, in the spirit of international collaboration, the French astronomer Joseph Lalande was able to use Cook's data to calculate the magical value for the Astronomical Unit - thus enabling the first reliable estimation of the distances of all the other planets from the Sun, and so fulfilling Edmond Halley's dream of measuring the "universe". The figure came to the astonishing value of just over 150 million kilometers, a figure very close to the modern accepted value of 149.6 million kilometers. Further minor refinements were made to the value during the transits that occurred in the 19th century.

As a side note story to this magnificent achievement, the British Admiralty, only ever mildly (at most) interested in the pursuit of scientific discovery, had seen another opportunity in Cook's "scientific" mission. In Tahiti Cook opened top secret instructions of the most sensitive nature. Once the mission in Tahiti was completed he would immediately set sail for the uncharted waters of the far Pacific. He would look for the

fabled continent of Nova Hollandia, known to Dutch (and probably the Portuguese) of the Seventeenth century, but never fully explored. He would chart the unknown eastern parts of a great land mass, known loosely as Terra Australis Incognita - the unknown Great Southern Land - and claim it for the British crown. We know this fabled land today as Australia.

Rare events are not always necessarily of little interest - on the contrary, it is often the rare events which can be of the most profound importance, as the lessons of the history of the measurement of the transit of Venus tells us. In kind, there are many rare medical diseases, but when their outcome may include death - then for the patient they are of the most extreme importance. We need at least to have a level of awareness about them if for no other reason than this - a case in point being that of the rare condition of Hereditary Angioedema.

Jeremiah Horrocks, the first person in history to witness a Transit of Venus; December 4 1639, Eyre Crowe, oil on canvas, 1891, Walker Gallery Liverpool.

HEREDITARY ANGIOEDEMA

Introduction

Hereditary angioedema (HAE) is a rare, but important genetic disorder that results from a deficiency in functional C1 inhibitor (C1-INH), either from:

- Low absolute levels

Or

- Production of dysfunctional protein.

The most serious manifestation is laryngeal swelling, which may result in fatal asphyxiation.

Trigger factors for attacks are recognized, but are often absent.

HAE does *not* respond to antihistamines, corticosteroids or adrenaline.

Definitive treatment requires the administration of C1-INH concentrate, or icatibant, a bradykinin receptor 2 antagonist and the main indication for this in the emergency setting will be any sign of laryngeal involvement, where the concentrate/icatibant must be given as soon as possible.

See also separate documents on:

- **Angioedema (in Allergy folder)**

- **Icatibant (in Drugs folder)**

History

The first description of HAE has been attributed to Robert Graves, who in 1843 described a patient with "a tumor rising on the forehead in the space of half an hour" and then later "sometimes the lips, inside of the mouth, palate and uvula are attacked, giving rise to a very considerable inconvenience".

The superceded term *angioneurotic edema* (a synonym for *angioedema*) is derived from Heinrich Quincke's original explanation that swelling arose from increased vascular permeability that could affect not only the face and larynx, but also the gastrointestinal tract.

The autosomal dominant nature of this disorder was described by William Osler, who reported the disorder in each of five family generations.

The biological basis for this disorder remained unclear until 1962, when Landerman suggested that HAE might result from dysregulation in kinin generation and that there might be an inherited defect in an inhibitor to a permeability factor such as kallikrein.

While investigating the properties of a newly discovered protein shown to inhibit C1 complement, Donaldson reported low circulating levels of this protein in patients with HAE.

Further studies by Rosen found that 85% of patients with HAE had low circulating levels of C1-INH (Type 1 HAE), with the remainder producing a dysfunctional inhibitor (Type 2)

Epidemiology

The precise prevalence of HAE in Australia is uncertain, but it is a rare condition.

There are no known ethnic or gender differences, with the exception of HAE Type 3, (mostly seen in females).

Pathology

In the absence of adequate levels of C1-INH, subcutaneous and submucosal oedema result from the *uninhibited action of vasoactive mediators*, of which **bradykinin** is considered the most important.

C1-INH is a serine protease inhibitor whose major activity is inhibition of a number of complement proteases and contact system proteases (plasma kallikrein and coagulation factor X11a).

During attacks of HAE, these plasma proteolytic cascades are activated and several vasoactive substances are released.

Three separate types of HAE are recognized:

- Type I:
  - ♥ Low circulating levels of C1-INH
  - ♥ This entity represents 85% of cases of HAE
- Type II:
  - ♥ Here there is normal C1-INH protein levels but impaired C1-INH protein *function.*
  - ♥ It represents around 15% of cases.
- Type III:
  - ♥ The very rare HAE Type 3 is *not* caused by C1-INH deficiency. It is caused by a mutation in the Factor XII gene and results in angioedema mainly affecting females. Factor XII *levels* in HAE Type 3 are normal and affected females do not exhibit abnormal clotting.

Acquired C1-INH deficiency (AAE) - not discussed in these notes, generally results from increased destruction or metabolism of C1-INH, due to an underlying disease process.

Complications:

- The most serious manifestation is laryngeal swelling, which may be fatal
- Affected patients also have higher than expected rates of autoimmune disease, (see below).

Genetics:

HAE is an **autosomal dominant** disorder.

Although a family history is usual, about 25% of newly diagnosed patients report no known affected family members.

In these patients a de novo mutation is presumed.

Members of the same kindred (with presumably the same genetic variant) may differ greatly in their expression of the disease (age of onset and frequency, severity and location of manifestations).

There is some evidence for increased frequency of autoimmune disorders in patients with HAE, such as glomerulonephritis, systemic lupus erythematosis, thyroiditis and inflammatory bowel disease.

Clinical features

HAE is characterized by **recurrent** attacks of swelling of:

- Subcutaneous tissues
- Gut
- Upper respiratory tract

Time course

Typically its time course takes **24 hours** to peak and then resolves over the ensuing **48-72 hours**, but may sometimes take longer than this to resolve.

Of more concern however are cases of much more rapid onset of laryngeal oedema.

Recurrences

Clinical episodes may occur frequently or may be some years apart.

50% of patients experience their first manifestation of the disease before the age of 10 years.

Pattern of attack:

HAE attacks in any one individual usually follow a typical - but not invariable - pattern.

Trigger factors:

Episodes of HAE can be precipitated by well recognized trigger factors, including:

- Stress (physical or emotional)
- Surgery (in particular head and neck and dental procedures).
- Hormonal factors:
  - ♥ Oral contraceptives, hormone replacement therapy and pregnancy.
- Drugs:
  - ♥ ACE inhibitors.

Often however no precipitating factor can be discerned.

Features

Features include:

1. Prodromal symptoms:

   Attacks may be preceded by a prodrome of:

   - Tingling

   Or

   - A non-itchy macular serpiginous rash (erythema marginatum) anywhere on the body.

     This is most often observed on the chest and may not be adjacent to the area of swelling.

     Note that urticaria is **not** a feature of HAE or other kinin-related forms of angioedema.

2. Oedema (**without urticaria**) of:

   - Face
   - Airway

♥ The most serious manifestation is **laryngeal swelling**, which may result in fatal asphyxiation.

Even though it accounts for fewer than 1% of episodes, more than 50% of patients report at least one occurrence of laryngeal angioedema at some stage in life.

Historical data suggest that mortality from laryngeal swelling was 30% prior to the introduction of effective prophylaxis.

Episodes of severe swelling are fortunately less common in children, but still do occur, and when it does complete obstruction can occur much more quickly compared to an adult, because of the relatively smaller calibre airway.

- Limbs
- Trunk
- Genitals

Importantly the cutaneous angioedema is *neither* itchy nor pitting

3. GIT:

- Visceral swelling of the gastrointestinal tract may result in abdominal pain, vomiting and diarrhea
- Hypotension may occur with this fluid loss
- Occasionally isolated abdominal pain can sometimes be the first and only manifestation of HAE in children.

Differential diagnosis:

For clinical features that will help differentiate HAE from other forms of angioedema, see appendix 1 below.

Investigations

Soft tissue neck x-rays:

These can assist in the assessment of the severity of airway narrowing.

C1-INH testing:

Testing for HAE should be carried out if there is a clinical suspicion in any age group

Testing should also be carried out if there is a positive family history.

Tests include:

- C4 levels (screening test):
    - ♥ In an untreated patient a normal C4 level makes the diagnosis of HAE unlikely.
- Specific tests for both C1-INH level and function are carried out.

In patients with isolated angioedema where clinical suspicion of HAE is low, screening with C4 levels may be adequate.

If HAE is strongly suspected, serum C4 *and* serum CI-INH level and function should be measured on at least two occasions. If doubt remains then measurements are made during an attack.

Genetic testing:

Mutations in the *SERPING1* gene that encode the C1-INH protein result in HAE Types 1 and 2 disease.

Genetic testing is not routinely required to establish diagnosis, but may be considered in cases presenting diagnostic uncertainty.

Now that genetic testing is available, prenatal diagnosis may be possible.

Management

Airway

The potential for airway obstruction must always be recognised and anticipated, and patients must be closely observed.

Early intubation is of course preferable to emergency surgical airway!

It should be noted that swelling of the tongue *on its own* seldom affects respiration but patients with tongue swelling should be monitored in case of progression to the airway.

Laryngeal swelling is not visible externally and may present as an isolated phenomenon in a patient who appears normal externally and even on examination of the oropharynx.

Symptoms that suggest laryngeal oedema in a patient with known HAE include:

- The sensation of a lump or fullness in the throat
- Voice change

- Dysphagia
- Stridor.

Patients must be encouraged to present **early** if any of these symptoms arise.

Indirect laryngoscopy is desirable for confirmation but is not necessary in a patient with known HAE

Direct laryngoscopy may cause increased swelling and should be avoided.

C1-INH concentrate or subcutaneous icatibant should be given as soon as possible, (see below).

Note that HAE does not respond to antihistamines, corticosteroids or adrenaline, although these will be used when the diagnosis is uncertain, as they will improve the symptoms of allergic IgE mediated cases of angioedema.

C1-INH concentrate

Definitive treatment requires the administration of C1-INH concentrate, or subcutaneous icatibant.

The main indication for this in the emergency setting will be any sign of laryngeal involvement, where medication must be given as soon as possible.

The C1-INH concentrate or icatibant may also be given for significant GIT symptoms.

Two brands of C1-INH are currently registered in Australia, (but neither are currently reimbursed and so must be access through hospitals). These are:

- **Berinert (a human C1 esterase inhibitor produced by CSL)**
- **Cinryze.**

If laryngeal symptoms are present C1-INH concentrate should be given *even if respiration does not seem to be threatened* since oedema can sometimes progress rapidly and C1-INH concentrate takes **30-90 minutes** to onset of action.

Lack of response after 60 minutes is an indication for a further dose.

Facilities and expertise for intubation should always be made available and because laryngeal oedema can make intubation difficult, tracheostomy or emergency cricothyrotomy may be required in extreme situations.

The dose is 20U/kg rounded up to the nearest full vial.

FFP

Historically, **fresh frozen plasma** has been used as a treatment modality for C1-INH replacement but with access to more specific treatment it has been superceded.

It may still be used in **emergency** settings **where no alternatives are available.**

However it carries the risk of blood borne infection, worsening the severity of the attack because of the inclusion of other biologically active molecules and the risk of reaction to it as a blood product.

Icatibant (Firazyr)

There is intense ongoing research in the development of effective specific **bradykinin receptor antagonists** to treat HAE, specifically the agent **icatibant.**

Subcutaneous administration will facilitate rapid use in emergency situations, and potentially allow home use and self-administration by patients.

There is additional potential for this agent to treat angioedema caused by *acquired* C1-INH deficiency and ACE-inhibitors.

It should be noted that whilst icatibant is an expensive drug, (as of February 2015 it is around 2,500 AUD a syringe), it can potentially save a patient from catastrophic airway compromise.

It should not be used for minor peripheral swellings, (though a patient should still be monitored closely).

It should be used for any tongue, neck, oropharyngeal, laryngeal swellings, and given its lag time of several hours to maximal effect, it should be given **early.**

Experience with cases of HAE also says that the earlier its use the more effective icatibant is, (*personal communication Professor Connie Katelaris February 2015*)

If it is a known case of ACE inhibitor induced angioedema or HAE then icatibant should also be given early for any potential airway problem.

If it is a de novo presentation then an initial trial of adrenaline first is indicated but if there is no response and increasing swelling, then it is reasonable to give empirical icatibant.

Disposition

A nine year old boy reportedly died of asphyxia 20 minutes after onset of swelling.

In comparison, severe laryngeal swelling in adults usually develops over 8 to 12 hours.

From these two points it is apparent that there must be close observation, especially in children, where life threatening symptoms can develop rapidly, and that there should be a period of observation of at least 12 hours.

Prophylactic considerations:

Short term prophylaxis is required to prepare patients for elective dental and surgical procedures involving the head and neck area.

Surgical and dental procedures may pose a special risk to patients with HAE and when possible, require planning and consultation between the **immunologist, anaesthetist and surgical teams.**

Some procedures such as those involving laryngopharyngeal manipulation or instrumentation, carry a much greater risk of triggering potentially life-threatening episodes.

Postoperative complications such as sepsis increase the risk of attacks during this period.

Reactions however are unpredictable, and patients should have prompt access to C1-INH concentrate whether or not they have received prophylaxis.

Prophylactic agents that are used include:

- Danazol:
- Tranexamic acid:
- C1-INH concentrate:

Long-term prophylaxis refers to the use of regular medication to prevent episodes of angioedema in those with confirmed HAE. The decision as to whether to institute long-term prophylaxis depends on individual factors such as the frequency of episodes, the severity and location of previous episodes, the presence or absence of known triggers and their avoidability, and the balance of these factors against the acceptability, cost and potential morbidity of prophylactic agents. **Consultation with an Allergy Specialist will be required.**

Care plans:

An individualised care plan giving indications of what to treat, when to treat and how to treat episodes should be produced for all patients who have HAE

This may be accompanied by a letter from the specialist so it may be given to any treating physician unfamiliar with the individual and the condition.

Ideally, a patient's local **emergency department** will have an **alert system** in place to fast track patients when they need to present there.

Patients should also have a **Medic Alert bracelet**, (or similar).

Appendix 1

Features distinguishing HAE from other forms of angioedema[10]

Symptom/Sign	HAE	Acquired	Allergic/IgE Mediated
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Age of onset (most frequent)	6-20	> 50	Anytime
Family history	Usually	No	Variable
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face and lips
Precipitation by trauma	Yes	Yes	No
Duration of swelling, hr	48-72	48-72	2-48
Response to treatment with epinephrine, antihistamine, corticosteroids	No	No	Yes

References

1. **Professor Connie Katelaris et al.** "Position Paper on Hereditary Angioedema", Australasian Society of Clinical Immunology and Allergy (ASCIA), Revised March 2011.

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