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SPECIAL REVIEW

Marathon of eponyms: 17 Quincke oedema (Angioedema)

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The use of eponyms has long been contentious, but many remain in common use, as discussed elsewhere (Editorial: Oral Diseases. 2009: 15; 185). The use of eponyms in diseases of the head and neck is found mainly in specialties dealing with medically compromised individuals (paediatric dentistry, special care dentistry, oral and maxillofacial medicine, oral and maxillofacial pathology, oral and maxillofacial radiology and oral and maxillofacial surgery) and particularly by hospital-centred practitioners. This series has selected some of the more recognized relevant eponymous conditions and presents them alphabetically. The information is based largely on data available from MEDLINE and a number of internet websites as noted below: the authors would welcome any corrections. This document summarizes data about Quincke's oedema.

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Quincke's oedema

Also known as
Angioedema
Bannister disease
Bannister syndrome
Milton urticaria
Milton–Quincke syndrome
Quincke disease
Quincke syndrome

The condition

Quincke oedema (angioedema) is a syndrome presenting with the sudden onset of painless, circumscribed, non-pitting swelling of the face (around the eyes, chin and lips), tongue, feet, genitalia and trunk, which persists from a few hours to 2 or 3 days and then resolves. Involvement of the upper airways can result in severe life-threatening symptoms, including the risk of asphyxiation, unless appropriate interventions are taken.

Angioedema may be hereditary or acquired; about half of the affected patients have no family history of angioedema. Hereditary angioedema (HAE) is an autosomal dominant disease that afflicts one in 10 000 to one in 150 000 people; HAE has been reported in all races, and no gender predominance has been found. HAE attacks are mediated by the generation of a vascular permeability enhancing factor, usually bradykinin, generated via contact system activation, which results in raised levels of bradykinin and cleaved high-molecular weight kininogen. Bradykinin is released on inappropriate activation of the contact system, which is controlled by C1 inhibitor (C1-INH) – a multifunctional serine protease inhibitor that is normally present in high concentrations in plasma. It is the only known plasma inhibitor of C1r and C1s, the activated proteases of the first component of complement. It is also the major plasma inhibitor of activated factor XII (Hageman factor), the first protease in the contact system. In addition, C1-INH is one of the major inhibitors of plasma kallikrein, the contact system protease that cleaves kininogen and releases bradykinin. A variety of host factors with roles in bradykinin metabolism and vasomotor activity explain the variable severity of the clinical presentation. HAE patients often have C1-inhibitor deficiency: the gene for C1-INH (*SERPING1*) mapping to 11q12-q13.1.

Three types of HAE have however, been described:

- Type I (85%) – low plasma levels of a normal C1-INH (low antigenic and functional plasma levels of a normal C1-INH protein). C1-INH deficiency allows autoactivation of C1, with consumption of C4 and C2.
- Type II – normal or raised levels of a dysfunctional C1-INH (normal or elevated antigenic levels of a dysfunctional mutant protein together with reduced levels of the functional protein). C1-INH deficiency allows autoactivation of C1, with consumption of C4 and C2.
- Type III (oestrogen dependent) – C1-INH is both qualitatively and functionally normal. C3 and C4 levels are normal. The exact mechanism of action

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responsible for the link between this type and oestrogen is via mutation in factor XII that allows for the inappropriate activation of the kinin cascade. In addition, these affected females have polymorphisms associated with lower levels of the major enzymes responsible for bradykinin degradation. Exposure to oestrogens in pregnancy or via drugs is an important precipitating factor of this type of angioedema.

Clinical features are identical in all types of HAE. Skin and visceral organs (respiratory and gastrointestinal) may be involved by the typically massive local oedema without concomitant pruritus, often resulting from one of several known triggers, including trauma (especially dental trauma), anxiety, menstruation, infection, exercise, alcohol consumption and stress. However, attacks can occur in the absence of any identifiable initiating event. Medications (e.g., oestrogen, angiotensin-converting enzyme [ACE] inhibitors and angiotensin II type 1 receptor antagonists) have also been shown to induce attacks. During pregnancy, symptoms may increase or decrease for HAE types I and II. In HAE type III, studies have reported first episodes or recurrences associated with oestrogen-containing oral contraceptives, oestrogen replacement therapy or pregnancy. As many as 2% of patients with HAE may have autoimmune disorders, such as systemic lupus erythematosus, glomerulonephritis, rheumatoid arthritis, thyroiditis, Sjögren syndrome and pernicious anaemia.

Acquired angioedema (AAE) has two recognized types:

- Type I (AAE-I) is associated with diseases which produce complement-activating factors, idiotype/anti-idiotype antibodies, or other immune complexes that destroy C1-INH function. These are mainly B-cell lymphoproliferative diseases which range from monoclonal gammopathies of uncertain significance (MGUS) to non-Hodgkin lymphoma (NHL). Neoplastic lymphatic tissue can consume C1-INH and the complement components of the classic pathway. Unlike those with HAE, patients with AAE have no family history of angioedema and are characterized by the late onset of symptoms due to the hypercatabolism of C1-INH. The reduction in C1-INH function leads to activation of the classical complement pathway and consumption of C1q followed by C2 and C4, as well as activation of the contact system, leading to the generation of the vasoactive peptide bradykinin, increased vascular permeability and angioedema.
- Type II (AAE-II) is an autoimmune process defined by an autoantibody against C1-INH which binds to the reactive part of C1-INH, impeding its regulatory capacity.

Acquired angioedema may be induced by a range of drugs. It occurs particularly in angiotensin-converting enzyme inhibitor (ACEI) users. Defective degradation of vasoactive peptide substrates of ACE, such as bradykinin or substance P, may contribute via non-ACE pathways to the pathogenesis of ACEI-associated angioedema. Bradykinin and des-arginine 9-bradykinin, two powerful vasodilatory and pro-inflammatory peptides, and substance P, substrates of angiotensin-converting enzyme, increase vascular permeability and cause tissue oedema in animals. Amino-terminal degradation of these peptides, by aminopeptidase P and dipeptidyl peptidase IV, may be impaired in individuals with ACEI-associated angioedema.

Orolingual angioedema is also a potentially life-threatening complication of alteplase treatment in stroke patients, especially in those using ACEI.

Angioedema may also be mediated by cytokines: examples include episodic angioedema with eosinophilia syndrome (Gleich syndrome), non-episodic angioedema with eosinophilia, NERDS (nodules, eosinophilia, rheumatism, dermatitis and swelling), Clarkson syndrome (idiopathic capillary leak syndrome) and angioedema associated with aldesleukin (human recombinant IL-2) and IFN-alpha. Anaphylaxis, angioedema or urticaria associated with eating beef, pork or lamb appear due to IgE antibodies to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate commonly expressed on non-primate mammalian proteins.

Quantitative and functional analyses of C1-INH (both antigenic and functional C1-INH), C4 and C1q should be performed when angioedema is suspected. Analysis of C1q can help differentiate between HAE and AAE caused by C1-INH deficiency.

Acute exacerbations of angioedema should be treated with intravenous purified C1 esterase inhibitor concentrate. Corticosteroids, antihistamines and epinephrine can be useful adjuncts, but are rarely efficacious in aborting acute attacks. Patients may be treated with attenuated androgen or antifibrinolytic agents. Intravenous fresh frozen plasma is also useful in acute HAE, but may occasionally exacerbate symptoms. Purified, virus-inactivated, human plasma-derived C1 inhibitor (C1-INH) concentrate; recombinant human C1-INH; Ecallantide, a potent kallikrein inhibitor; and Icatibant, a bradykinin 2 receptor antagonist, are becoming available for treatment. When respiratory obstruction is present, there is a major clinical dilemma; endotracheal intubation or tracheostomy adds to the trauma and may exacerbate the angioedema, although it may be essential to preserve the airway.

Background to eponym

The first description of angioedema was by Marcello Donati in 1586. John Laws Milton described it in 1876 as 'giant urticaria' and in 1882 Quincke further described the condition, as did Henry Martyn Bannister in 1894.

The persons

Heinrich Irenaeus Quincke was born on 26 August 1842, in Frankfurt an der Oder, Germany. He studied Medicine at Heidelberg, Würzburg and Berlin, with

Rudolf Virchow, Albert von Kölliker and Hermann Helmholtz. He obtained his doctorate at Berlin in 1863. He then moved to Vienna and, in 1866, became an assistant to Robert Ferdinand Wilms at Diakonissenhaus Bethanien. From 1867 to 1871, he was an assistant with Friedrich Theodor von Frerichs at Berlin Charité. Quincke was habilitated (achieved the highest academic qualification) for internal medicine at Berlin in 1870. In 1873, he was appointed to the Chair of internal medicine at the University of Bern and after 5 years, he moved to the Chair at the University of Kiel where he remained until his retirement in 1908 to Frankfurt am Main.

Quincke's most notable contribution was to introduce the lumbar puncture. He died on 19 May 1922, in Frankfurt am Main.

Henry Martyn Bannister was born on 25 July 1844, in Cazenovia, New York, USA. He received his doctorate in 1871 at the National Medical College (now George Washington University) in Washington. He founded the Quarterly Journal of Nervous and Mental Diseases with James Stewart Jewell in 1874. He died on 1 May 1920, in Evanston, Illinois.

John Laws Milton was born on 30 November 1820, in Bishopwearmouth, UK. He studied at Edinburgh, London, Paris and Vienna, becoming a member of the Royal College of Surgeons of England in 1843. He settled in London in 1850, became a surgeon and lecturer in skin diseases in 1863 and died in 1898.

Associated persons

Henry Martyn Bannister
John Laws Milton
Heinrich Irenaeus Quincke

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