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Abstract

The origins of the discovery of the “Complement System” date from the second half of the nineteenth century. The official paternity of the Complement System is attributed to Jules Bordet. The complement system can be activated through three major pathways: the classical pathway, the alternative pathway, and the lectin pathway converge in a common final lytic pathway. Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency (C1-INH-HAE) was first described by Robert Graves in his clinical lectures. The autosomal dominant pattern of HAE was recognized by Sir William Osler. The pathophysiologic basis of C1-INH-HAE as a deficiency of a plasma inhibitor was discovered in the early 1960s. In 1986, the C1NH gene was identified, which encodes the C1-INH protein. Although the possible relationship between angioedema and estrogens in women was described as early as 1986, it was not until the first decade of the twenty-first century when several series of patients with HAE were described with normal levels of the fractions of the complement system. In the last decade, several drugs have been approved and marketed in Europe, in the United States, and in other countries, contributing to the improved management of C1-INH-HAE and patient’s quality of life.

Keywords: acquired angioedema, angioedema, bradykinin, C1 inhibitor, complement system, factor XII, hereditary angioedema, hereditary angioedema with mutation in F12 gene, history, immunodeficiency
1. Introduction

The origins of the discovery of the “Complement System” date from the second half of the nineteenth century. The official paternity of the Complement System is attributed to Jules Bordet. The complement system can be activated through three major pathways. The classical pathway, the alternative pathway, and the lectin pathway converge in a common final lytic pathway. This chapter describes the historical discovery of biochemistry pathways implicated in the pathophysiology of bradykininergic angioedema (BK-AE).

2. Historical review of the Complement System

The origins of the discovery of the “Complement System” date from the second half of the nineteenth century. In that era, the works of Louis Pasteur (1822–1895), Robert Koch (1843–1910) [1], and Joseph Lister (1827–1912) [2] contributed to the knowledge needed to consider many microorganisms as producers of lethal effects in humans. It was obvious that the human body, despite being constantly exposed to microorganisms, successfully overcame their assaults, discovering that many of them were destroyed in the blood, one of whose effector systems of defense was the “complement system” [3] (Figure 1).

Taube and Gscheidlen made one of the first observations that the blood of various mammals possessed bactericidal activity [4]. These authors injected microorganisms in the bloodstream, sampling at 24 and 48 hours while preserving them aseptically. Even months after storage, bacterial multiplication was not observed. Wyssokowitsch [5] and von Fodor [6, 7] repeated the experiment, injecting microorganisms in the blood of mammals, noting that within minutes there were no viable organisms; they thought that they had been cleared by the blood cells. Metschnikoff [8] found phagocytes that engulfed and destroyed microorganisms, but soon discovered that blood cells were not solely responsible. Grohmann [9] was the first scientist who discovered that in vitro plasma (cell-free) was capable of lysing bacteria and fungi.

Nuttal [10], in experiments similar to those conducted previously by Wyssokowitsch [5] and von Fodor [6, 7], observed morphological changes in microorganisms (anthrax bacillus) that had escaped phagocytosis, concluding that they had been damaged by a noncellular process. After inoculating defibrinated sheep blood with bacteria, the bactericidal activity was preserved both in vivo and in vitro, but disappeared if the blood was heated to 45°C or was stored for several days at room temperature. A year later, Buchner [11, 12] reported that fresh serum was able to lyse bacteria, but if heated for 30 minutes at 55°C, this capacity was lost. He also found that the dialysis of fresh serum against water at 0°C for 18–36 hours abolished the lytic activity, but there was no loss when dialyzed against bicarbonate buffer containing 0.75–0.8% NaCl. He called fresh factor serum with bactericidal activity “alexina,” concluding that it was due to proteins with enzymatic activity.

Pfeiffer and Issaef [13] reported that the activity of alexina was due to the joint action of specific antibodies and specific serum factor. In their experiment, the blood of guinea pigs that recovered from cholera infection protected normal guinea pigs if they were injected alexina
Figure 1. Historical review of the Complement System (from 1850 to 1930) [3].
mixed with live bacteria. *In vitro* data showed that vibrios were eliminated only by fresh immune serum, but not by heat-inactivated immune serum. Protection against cholera present during injections of heat-inactivated immune serum was due to the antibody. Therefore, bacterial lysis was due to the association of the antibody plus complement. Bacteriolytic ability of serum from animals immunized with a particular microorganism was higher than that of animals immunized against this microorganism.

The official paternity of the Complement System is attributed to Jules Bordet, who performed the critical experiments that identified the "complement system" in 1894 [14, 15]. Bordet [16, 17] showed that increased immune serum bactericidal activity was due to the action of two factors [3]:

(a) Thermostable factor increased by immunization, specifically reacting with the microorganism used to immunize.

(b) Thermolabile factor present in normal and immune sera, nonspecific (at least in the way the thermostable factor was). Bordet quickly identified such a factor with the bactericidal activity or alexina described by Buchner [11, 12]. He was also able to lyse erythrocytes sensitized with specific antibodies against erythrocyte antigens.

Ferrata [18] showed that the complement consisted of several serum factors that could be separated by physicochemical means, but it was Brand [19] the following year who best characterized both fractions [3]:

(a) He called the activity in the precipitate (euglobulins) “mid-piece” because he found that it acted after the antibody (front-piece) would bind to the cell (RBC).

(a) He called the activity in the supernatant (pseudo-globulins) “end-piece” because it acted only after the “mid-piece” had acted.

(b) Interaction of erythrocytes with the antibody, mid-piece, and end-piece, in that order, produced hemolysis.

Brand’s works established a number of assumptions:

(a) The action of the complement is sequential.

(b) An intermediate product as a function of hemolysis was generated.

Both the mid-piece and the end-piece are temperature sensitive.

2.1. Historical development of the classical complement pathway

Ritz [20] and Coca [21] were the first to demonstrate the existence of a third component other than the mid- and end-piece following observation of the destructive effect of cobra venom on the complement [3] (*Figure 2*). Coca treated fresh serum with yeast, concluding that the third component was capable of combining with yeast and he called it C′3. Gordon et al. [22] showed a fourth component, which he called C′4 when observing that the ammonium destroyed a thermostable
Figure 2. Historical review of the discovery of the Complement System (from 1930 to 1985) [3].
factor from serum other than C3 (the mid-piece was called C1 and the end-piece was renamed C2). It should be noted at this point that C1 and C2 do not correspond to the current fractions C1 and C2, since both constitute the full complement including C3 and C4. Ueno [23] established the order of performance of the components known up to that time. Pillemer [24] managed to separate the four serum fractions into different components and set the activation sequence C1, C4, C2, and C3. It was not until the early 1960s, once chromatographic methods were developed, that the various components could be purified. Nelson [25, 26] showed that in reality the third component C3 was formed by at least six factors (C3c, C3b, C3e, C3f, C3a, and C3d). Having established that these were proteins not related to C3 acting at a later stage, he called them C5, C6, C7, C8, and C9, respectively. As of 1968, World Health Organization (WHO) annulled the symbol “′” leaving it currently C1, C2, and so on.

2.2. Historical development of the alternative complement pathway

The heavy reliance of the study of the classical complement pathway using erythrocytes sensitized with antibodies for activation did not even consider the possibility of activation by other substances [3]. However, since the early twentieth century, there were data suggesting that it was possible to lyse erythrocytes with cobra venom without antibodies and with the participation of various components other than those of the classical pathway. Pillemer [27] was the father of the discovery of the alternative pathway upon describing a protein or a new component called “properdin,” which when absent diminished the bactericidal potency of serum against certain bacteria.

2.3. Historical development of the final common lytic complement pathway

Green et al. [28] suggested that the cytolysis mediated by complement involved the production of pores in the cell membrane on the grounds that large molecules ( dextrans and albumin) prevented cell lysis when present in high concentration in the reaction medium; on the contrary, but small molecules did not not [3] (Figure 2). Cell rupture was thought to be due to a colloid-osmotic swelling process that finally finished by lysing the cell. Borsos et al. [29], with the use of electron microscopy, visualized ultrastructural lesions etched into cell membranes, showing that the lesions were associated with the cytolitic complement activity. Lachman [30] showed that the five terminal components C5, C6, C7, C8, and C9 were necessary and sufficient to cause such lesions. Haxby [31] and Kinsky [32] were the first to demonstrate that the lipid bilayer was the target of the “membrane attack complex” (MAC), noting that C5-C9 directly damaged the integrity of the bilayer without any enzymatic activity. Mayer [33] formulated the “donut hypothesis” where cell damage is achieved through the formation of a structure described as a donut, forming stable transmembrane pores. Lysis would be explained by the osmotic difference between the exterior and the interior cell through the transmembrane channel. Bhadki [34] and Podack [35] observed that the MAC was due to C5-C9 multimolecular assembly. Bieseeker [36] initially postulated a dimeric structure (C5-9)2, but Bhakdi [37] suggested a monomeric complex with the same structure as the complex SC5b-9 (“S” was one of the proteins that control the MAC). The C9 alone forms complexes structurally similar to the full MAC [38].
3. Historical review (from C1 inhibitor to bradykinin)

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency (C1-INH-HAE), also known as “non-allergic angioneurotic edema,” “AE without urticaria,” or “Osler’s hereditary edema” is a potentially fatal clinical entity, which in recent years has become an example to be followed because of the great progress made from the union of researchers, physicians, and patient associations worldwide (Figure 3).

It was first described in 1843 by Robert Graves in his clinical lectures. In 1882, Heinrich Quincke documented some cases of acute, circumscribed edema, involving two generations of the same family and coined the term angioneurotic edema [39]. Subsequently, Sir William Osler in 1888 first described in detail an inherited form of angioedema (AE) [40], from which in 1917 the hereditary type was identified [41]. The disease was defined biochemically in 1963 by Donaldson and Evans [42], as an absence of serum inhibitor of the first component of the complement. Dating from 1972 is the first case of acquired angioedema due to C1 inhibitor deficiency (C1-INH-AAE) in lymphosarcoma [43].

The main symptom of C1-INH-HAE is the attack of AE, the laryngeal location being the most serious. Landerman [44] reviewed all the medical literature published between 1888 and 1962 and found 28 publications of more than one case of death from fatal laryngeal attacks in more than one family with C1-INH-HAE. The total number of deaths due to C1-INH-HAE was 92.

In 1960, Spaulding demonstrated the efficacy of methyl testosterone in the treatment of C1-INH-HAE in a family [45]. In 1976, a double-blind placebo-controlled trial demonstrated the efficacy of danazol for the treatment of C1-INH-HAE [46]. It was then when stanozolol, another attenuated androgen, started to be used [47].

In 1968, the first case of C1-INH-HAE successfully treated with epsilon-aminocaproic acid (EACA) was published [48], although it was not until 1972 when the efficacy of anti-fibrinolytic agents (AFs), EACA, and tranexamic acid was demonstrated in double-blind clinical trials [49, 50]. AFs are reserved for those patients who cannot tolerate attenuated androgens or present contraindications for their administration.

An article published in 1973 described for the first time the administration of concentrated C1-INH (pdC1INH), partially purified from a mixture of human plasma, in two patients [51]. Previously, replacement therapy in patients with C1-INH-HAE in the attack phase had been attempted with fresh-frozen plasma [52], which was abandoned later because of the risk of viral transmission, although it was still used in case of pdC1INH being unavailable [53].

In the USA, two double-blind placebo-controlled clinical trials had been conducted with pdC1INH, which had proven its efficacy and safety [54]; however, the Food and Drug Administration (FDA) had not yet approved its use in the 2000s. At that time, Berinert® (Behring, Marburg, Germany) was commercialized in Germany and a few European countries [55] and was available in Spain, where it was imported through the Foreign Medicines service [56].
In 1986, the C1NH gene was identified (Gene Bank X54486; Swiss-Prot P05155), which encodes the C1INH protein, also called SERPING1, located on chromosome 11 subregion q11-q13.1 [57–59]. Although the possible relationship between AE and estrogens in women was described as early as 1986 [60], it was not until the first decade of the twenty-first century when several series of patients with HAE were described with normal levels of the fractions of the complement system [61, 62]. It was originally called HAE type III [62]. Finally, a mutation was found in F12 gene in some of the families [63–65].

Initially, C2-kinin, a vasoactive peptide generated by cleavage of the C2b fragment was thought to be involved in angioedema formation in C1-INH-HAE [66].

In 1998, there was growing support for another hypothesis in the generation of AE. It argued that BK was the most important mediator in the development of AE [67] and had been proven through clinical, in vitro studies and experiments in an experimental model of C1INH-deficient transgenic mice [68]. In 2002, a transgenic mouse with C1 inhibitor deficiency was developed by Professor Davis [69].
In the last decade, several drugs have been approved and marketed in Europe, in the United States, and in other countries, contributing to improved management of C1-INH-HAE and patient’s quality of life.

First, icatibant acetate (Firazyr®, Shire HGT, Zug, Switzerland) [70, 71], a bradykinin B2 receptor blocker, was approved by the European Medicines Agency (EMA) in 2008 for the treatment of acute AE attacks in adult patients with C1-INH-HAE [72] and was marketed in Spain in March 2009.

In 2008, a new C1-esterase inhibitor formulation, Cinryze®, was approved by FDA for the long-term prophylaxis of C1-INH-HAE [73]. This drug incorporated a nanofiltration step as an extra safety procedure to reduce the transmission of enveloped and nonenveloped viruses and possible prions [74, 75] and had been shown to be effective in reducing the number of AE attacks per month [76, 77]. In 2011, the European Medicines Agency (EMA) approved the marketing of Cinryze® for long-term prophylaxis, but also for short-term prophylaxis and treatment of acute AE attacks in adults and adolescents with C1-INH-HAE [78].

Berinert®, which had been marketed in Germany in 1985, was approved in 2008–2009 in different European countries through a mutual recognition agreement for the treatment of acute AE attacks in children and adults with C1-INH-HAE. Later, it also incorporated the nanofiltration step and it was approved by the EMA for short-term prophylaxis in children and adults in 2013 [79]. In 2009, FDA approved Berinert® for the treatment of acute abdominal and facial AE attacks in adolescents and adults with C1-INH-HAE [80].

In December 2009, Ecallantide (DX-88, Kalbitor®, Dyax Corp, currently part of Shire HGT), a kallikrein inhibitor, was approved by the FDA for the treatment of acute AE attacks in patients >16 years with C1-INH-HAE [81]. It was later approved for adolescents (2014).

A recombinant C1 inhibitor (rhC1INH) (Ruconest®, Pharming Technologies BV®, Leiden, The Netherlands) produced in transgenic rabbits [82] was approved by EMA in 2010 for the treatment of acute AE attacks in adult patients with C1-INH-HAE [83]. It was in 2014 when the FDA approved it for the same indication by FDA [84].

Some European centers have developed training programs for self-administration of intravenous and subcutaneous specific drugs for the treatment of C1-INH-HAE [85–90].

The development of new drugs or new uses for old drugs changed the therapeutic approach in C1-INH-HAE in the last decade. However, the development of new drugs will even alter more therapeutic landscape for C1-INH-HAE in the next years.

4. Historical review (from C1 inhibitor to coagulation factor XII)

In hereditary angioedema (HAE) with mutation in F12 gene (FXII-HAE), symptoms are similar to C1-INH-HAE, there are no abnormalities in the C1NH gene and antigenic and functional C1INH, C1q and C4 are usually within the normal range [91]. The final common mediator is thought to be bradykinin (BK). The history of the description of nC1-INH-HAE can be seen in Figure 4.
Figure 4. Historical review of angioedema type III.
In 2000, Binkley et al. [92] analyzed the family tree of eight women from three different generations noting that AE episodes were triggered by estrogen treatment (OCPs, hormone replacement therapy in menopause) or by pregnancies, the onset being at 14–21 days after conception, and at 7–14 days after the initiation of hormone replacement therapy. Börk et al. [93] described simultaneously a series of 36 women with angioedema with functionality conserved in the different fractions of the complement system (including C1 inhibitor), and who worsened in relation to situations of increased estrogens. Bork et al. [93] proposed to call this new AE type as HAE type III. Simultaneously, Marcos et al. [94] described in the XXII National SEAIC Congress the first family case in Spain, data that would be extended over the years [95]. One year later, Martin et al. [96] contributed data regarding the transmission of “HAE type III” in France.

Boulliet et al. [97] reported that increased levels of estrogen in healthy women have produced a reduction of C1INH, which entailed an increase in amidolytic FXII activity. Dewald et al. analyzed 20 unrelated women with HAE without C1INH deficiency, finding two mutations in the F12 gene in the second position of the ACG codon, corresponding to the residual amino acid 309; mutation I (five patients) 1032C>A; Thr309Lys; and mutation II (1 patient) 1032C>G; Thr309Arg (Figure 4). This mutation was not found in 145 healthy controls. Later, these authors extended the study to five families with 20 symptomatic patients and 10 asymptomatic family members (eight men and two women), which showed the presence of one of the two mutations [98]. Cichon et al. [99] studied a family proving that the increased amidolytic enzymatic activity of FXII in women produced an increase in the production of kinins. A year later, Martin et al. [100] studied four generations of one family with eight members who were carriers of the F12 gene 1032C>A mutation (four symptomatic and four asymptomatic), noting that in women symptoms were triggered or exacerbated by estrogens, whereas in men the symptoms were milder.

Börk et al. [101] described 35 symptomatic women from 13 different families with FXII-HAE (with proven mutations p.Thr309Lys/p.Thr309Arg). Triggers were taking OCPs (17 women) and pregnancy (3 women). A symptomatic exacerbation occurred after taking OCPs (8 women), pregnancy (7 women), hormone replacement therapy with estrogen (3 women), taking ACE inhibitors (2 women) and taking type 1 ACE receptor blocker (1 woman). pdC1INH was effective as the treatment of acute AE attacks (6 women) and progestogens (8 women), danazol (2 women), and tranexamic acid (1 woman) were used as prophylactic treatment.

Börk et al. proposed to use FXII-HAE to name those cases of nC1-INH-HAE with a mutation in F12 gene and unknown-HAE (U-HAE) to those without a known mutation [101].

The series with the largest number of hereditary (related to estrogen) (HAE type III) corresponds to Börk et al., who described 69 patients from 23 unrelated families with HAE-FXII, and 196 patients with U-HAE [102].

An increase in FXII amidolytic activity was initially described as the cause of activation of contact system and the final release of bradykinin with the consequent angioedema in FXII-HAE [99], although other authors could not confirm this. Recently, another study has shown
that the different mutations in exon 9 of \textit{F12} gene found in FXII-HAE produce an increase in FXII activability by plasmin \cite{103}.

In Spain, several studies have been published focusing on FXIII-HAE: Serrano et al. \cite{104} (six cases; two of them women from the same family) and Prieto et al. \cite{105} (four generations of the same family with mutation 1032C>A; Thr309Lys; three symptomatic women, one male asymptomatic carrier).

Baeza et al. \cite{106} described a nonatopic 27-year-old Arab woman from Morocco with a clinical diagnosis of hereditary angioedema type III and the p.Thr328Lys mutation. Icatibant acetate was prescribed for compassionate use.

Gómez-Traseira et al. \cite{107} describes 20 cases (11 females and 9 males on a large 3-generation Spanish family). The p.Thr309Lys mutation was detected in five female patients who had a phenotypic variant in which AE was exclusively precipitated by high estrogen levels and in six asymptomatic relatives.

Piñero-Saavedra et al. \cite{108} described p.Thr309Lys mutation in 35 individuals (80% females) from 9 unrelated families. In this prospective observational cohort study, 16 females (44% estrogen dependent, 56% estrogen sensitive) were clearly symptomatic. Also, two polymorphisms (XPNPEP2 c-2399A and the ACE insertion/deletion) were detected in 17% of patients.

The University Hospital in Grenoble is a reference center for the study of FXII-HAE in France. As a result of this, Vitrat-Hincky et al. \cite{109} published a retrospective analysis (for the years 2000–2009) with 26 patients, which included four symptomatic men.

Duan et al. \cite{110} not only confirmed the \textit{F12} gene mutation (gene-codifying coagulation factor XII) in women of the same family but also provide certain polymorphisms in the genes encoding aminopeptidase P (APP) and angiotensin-converting enzyme (ACE). It highlights the role of the BK-catabolizing enzymes in the pathogenesis of angioedema.

Börk et al. \cite{111} described a new mutation in the \textit{F12} gene (deletion of 72 base pairs c.971_1018+24del72*). More recently, Kiss et al. \cite{112} described a new mutation consisting in the duplication of 18 base pairs (c.892_909dup) causing the repeated presence of 6 aa (p.298-303) in the same region of FXII to those described above.

Grumach et al. \cite{113} report two Brazilian FXII-HAE families segregating the mutation c.983 C>A (p.Thr328Lys). In each family, one patient with a homozygous mutation was found. The homozygous FXII-HAE mutation status leads to a severe phenotype in females and males, and to an increased risk of manifest symptoms in the latter.

In terms of treatment, there is no approved drug for the treatment of nC1-INH-HAE, either FXII-HAE or U-HAE. The pdhC1INH has been used in the acute attack of AE in some cases of FXII-HAE \cite{102, 114, 115}. More recently, icatibant acetate was effective but also used off-label as this indication is not reflected in the product’s prescribing information \cite{115}.
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