Chapter 14

Bradykinin-Mediated Angioedema Across the History

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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 Issaeff [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

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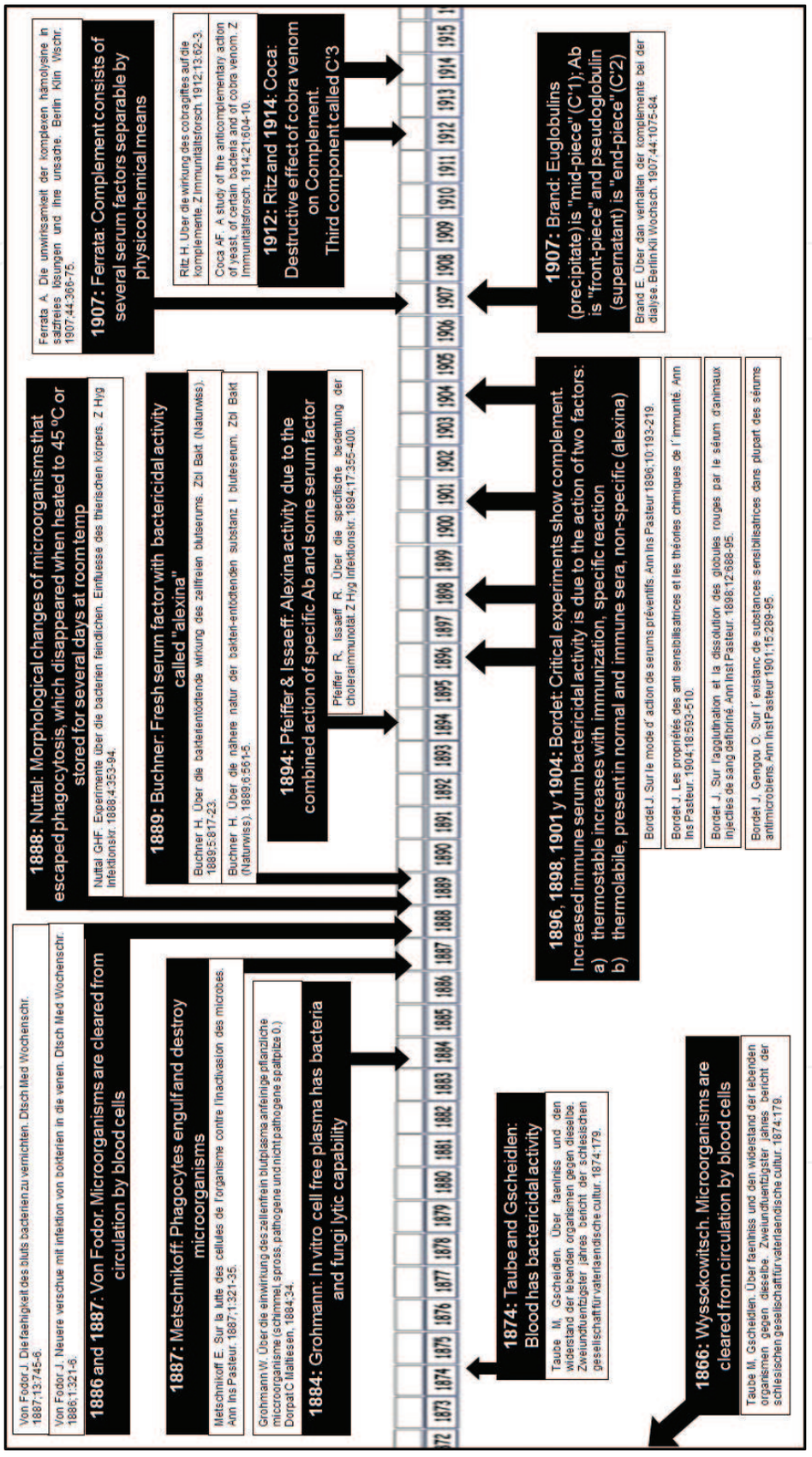

Figure 1. Historical review of the Complement System (from 1850 to 1930) [3].

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

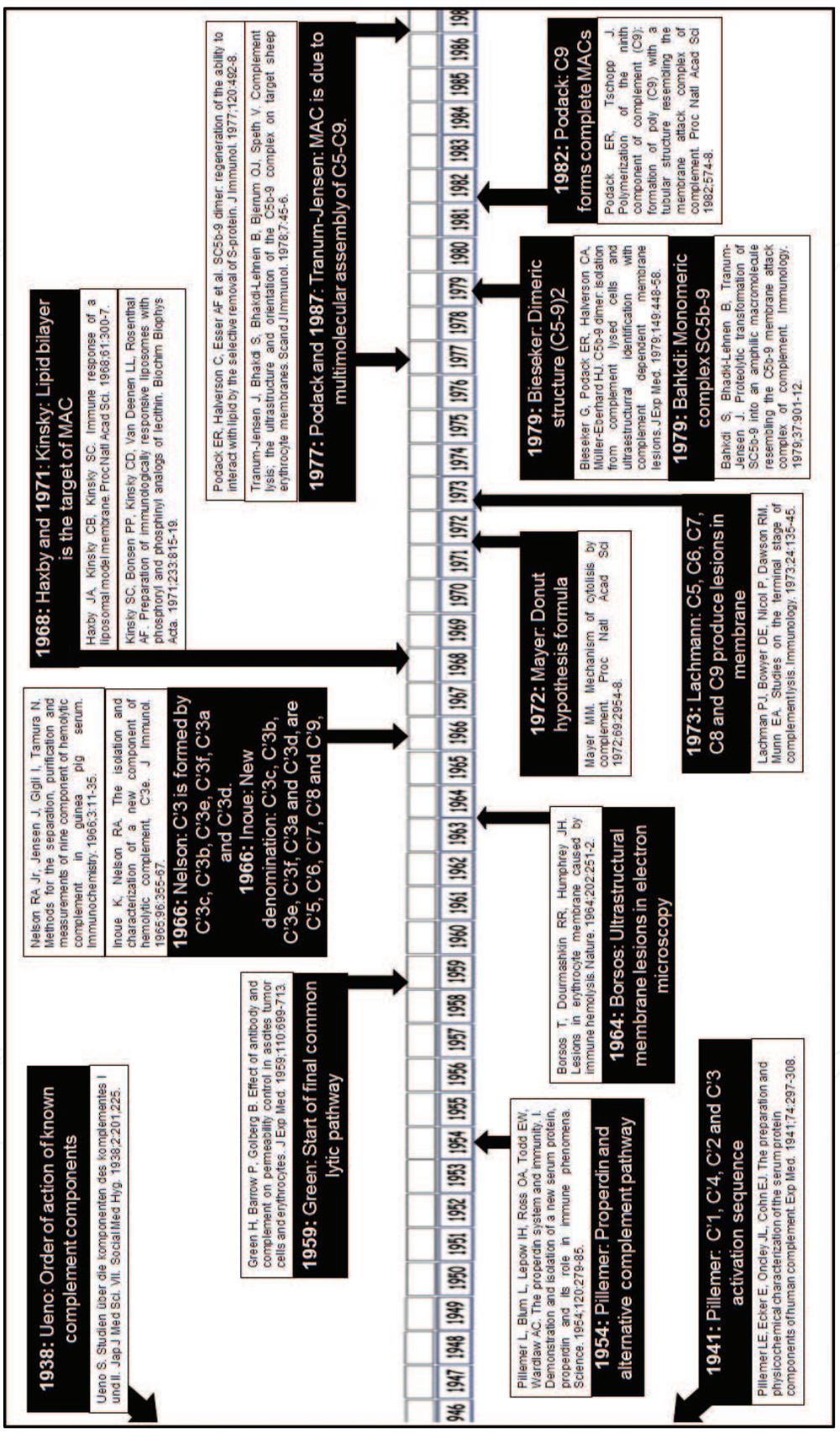

Figure 2. Historical review of the discovery of the Complement System (from 1930 to 1985) [3].

factor from serum other than C′3 (the mid-piece was called C′1 and the end-piece was renamed C′2). It should be noted at this point that C′1 and C′2 do not correspond to the current fractions C1 and C2, since both constitute the full complement including C′3 and C′4. 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 C′1, C′4, C′2, and C′3. 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 C′3 was formed by at least six factors (C′3c, C′3b, C′3e, C′3f, C′3a, and C′3d). Having established that these were proteins not related to C′3 acting at a later stage, he called them C′5, C′6, C′7, C′8, and C′9, 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 [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 cytolytic 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. Bieseker [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].

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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-P® (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].

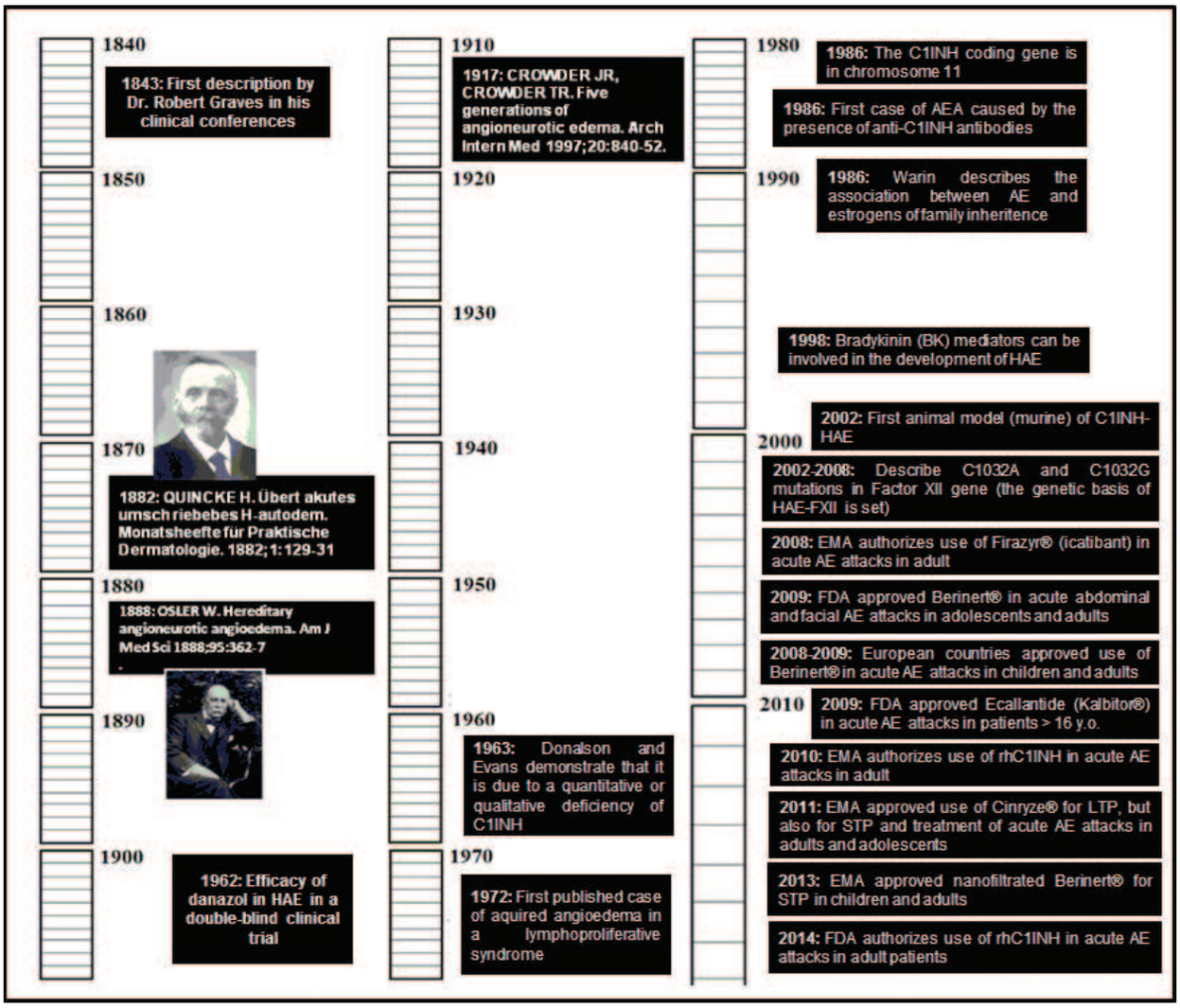

Figure 3. Historical review of angioedema due to C1-inhibitor deficiency.

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**.

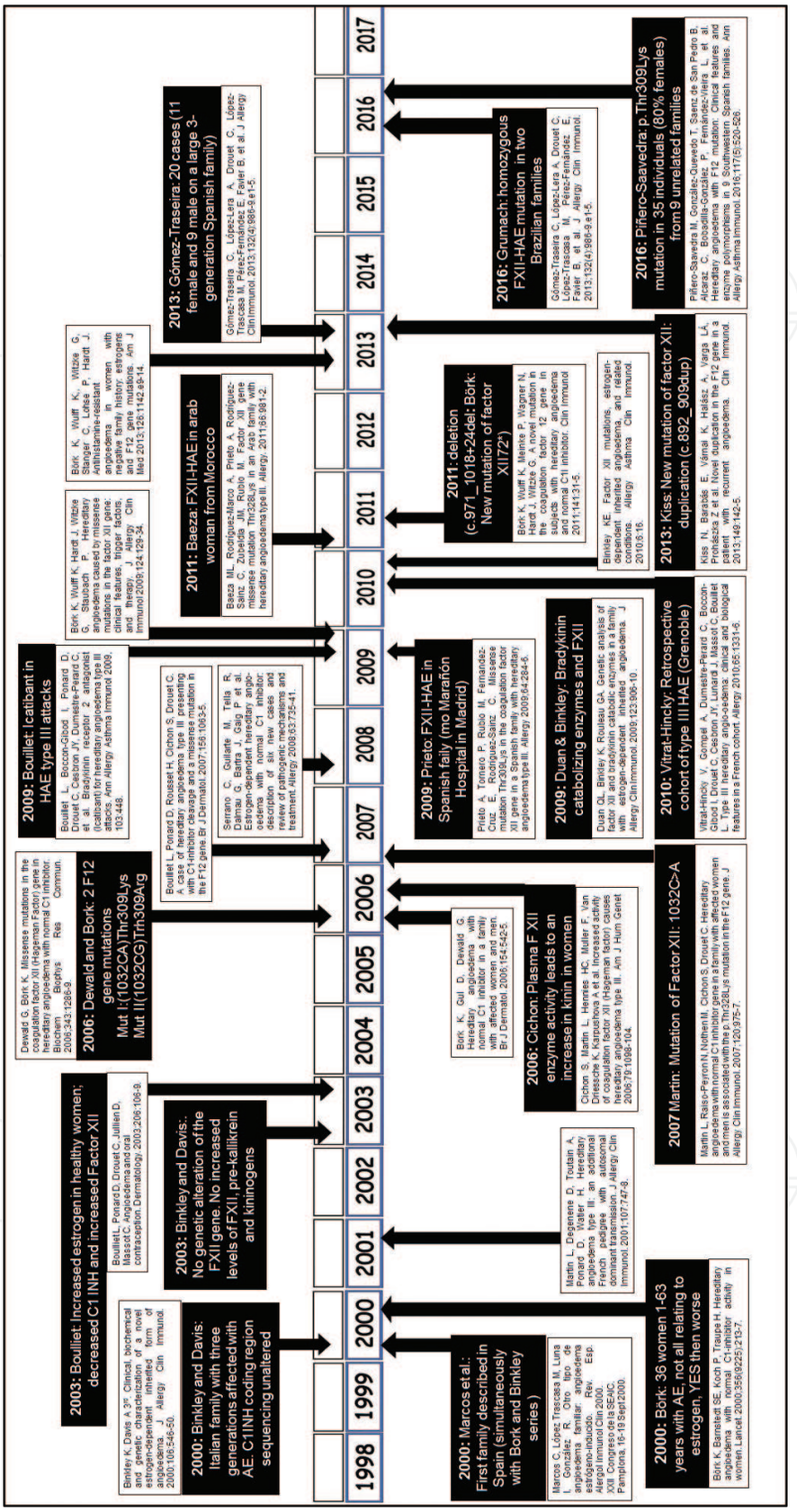

Figure 4. Historical review of angioedema type III.

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 *F12* gene found in FXII-HAE produce an increase in FXII activability by plasmin [103].

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

Baeza et al. [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. [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. [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. [109] published a retrospective analysis (for the years 2000–2009) with 26 patients, which included four symptomatic men).

Duan et al. [110] not only confirmed the *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. [111] described a new mutation in the *F12* gene (deletion of 72 base pairs c.971_1018+24del72*). More recently, Kiss et al. [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. [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 [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 [115].

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References

[1] Koch R. UntersuchungenüberBakterien: V. Die ätiologie der Milzbrand-Krankheit, begründetauddieentwicklungsgeschichte des *Bacillus anthracis*. [Investigations into bacteria: V. The etiology of anthrax, based on the ontogenesis of *Bacillus anthracis*]. CohnsBeitragezurBiologie der Pflanzen. 1876;2:277–310.

[2] Bankston J. Joseph Lister and the Story of Antiseptics (Uncharted, Unexplored, and Unexplained). Bear: Mitchell Lane Publishers. 2004. ISBN: 1-58415-262-1.

[3] Vivanco Martínez F. Hundred years of complement (Cien años de complemento). Immunology (Inmunología). 1990;9:99–107.

[4] Taube M, Gscheidlen. Über faenlniss und den widerstand der lebenden organismen gegen dieselbe. Zweiundfuenfzigster jahres bericht der schlesischen geselischaft für vaterlaendische cultur. 1874:179-95.

[5] Wyssokowitsch W. Über die schicksale der in´s blut injicierten mikro-organismen in Körper der warmblüter. Z Hyg Infektionskr. 1866;1:3–9.

[6] Von Fodor J. Neuere verschue mit infektion von bokterien in die venen. Dtsch Med Wochenschr. 1886;1:321–6.

[7] Von Fodor J. Die faehigkeit des bluts bacterien zu vernichten. Dtsch Med Wochenschr. 1887;13:745–6.

[8] Metschnikoff E. Sur la lutte des cellules de l'organisme contre l'inactivasion des microbes. Ann Ins Pasteur. 1887;1:321–35.

[9] Grohmann W. Über die einwirkung des zellenfrein blutplasma anfeinige pflanzliche miccroorganisme (schimmel, spross, pathogene und nicht pathogene spaltpilze 0.) Dorpat C Maltiesen, 1884;34-45.

[10] Nuttal GHF. Experimente über die bacterien feindlichen. Einfluesse des thierischen körpers. Z Hyg Infektionskr. 1888;4:353–94.

[11] Buchner H. Über die bakterientödtende wirkung des zellfreien blutserums. Zbl Bakt (Naturwiss). 1889;5:817–23.

[12] Buchner H. Über die nähere natur der bakteri-entödtenden substanz I bluteserum. Zbl Bakt (Naturwiss). 1889;6:561–5.

[13] Pfeiffer R, Issaeff R. Über die specifische bedentung der choleraimmunotät. Z Hyg Infektionskr. 1894;17:355–400.

[14] Bordet J. Sur le mode d'action de sérums préventifs. Ann Ins Pasteur. 1896;10:193–219.

[15] Bordet J, Sur l'agglutination et la dissolution des globules rouges par le sérum d'animaux injecties de sang defibriné. Ann Inst Pasteur. 1898;12:688–95.

[16] Bordet J, Gengou O. Sur l'existence de substances sensibilisatrices dans plupart des sérums antimicrobiens. Ann Inst Pasteur. 1901;15:289–95.

[17] Bordet J. Les propriétés des anti sensibilisatrices et les théories chimiques de l´immunité. Ann Ins Pasteur. 1904;18:593–510.

[18] Ferrata A. Die unwirksamkeit der komplexen hämolysine in salzfreies lösungen und ihre unsache. Berlin Klin Wschr. 1907;44:366–75.

[19] Brand E. Über dan verhalten der komplemente bei der dialyse. Berlin Kli Wochsch. 1907;44:1075–84.

[20] Ritz H. Uber die wirkung des cobragiftes auf die komplemente. Z Immunitältsforsch. 1912;13:62–3.

[21] Coca AF. A study of the anticomplementary action of yeast, of certain bacteria and of cobra venom. Z Immunitältsforsch. 1914;21:604–10.

[22] Gordon J, Whitehead KR, Wormall A. The action of ammonia on complement. The fourth component. J Biochem. 1926;20:1028–35.

[23] Ueno S. Studien über die komponenten des komplementes I und II. Jap J Med Sci. VII. Social Med Hyg. 1938;2:201–225.

[24] Pillemer LE, Ecker E, Oncley JL, Cohn EJ. The preparation and physicochemical characterization of the serum protein components of human complement. Exp Med. 1941;74:297–308.

[25] Nelson RA Jr, Jensen J, Gigli I, Tamura N. Methods for the separation, purification and measurements of nine component of hemolytic complement in guinea pig serum. Immunochemistry. 1966;3:11–35.

[26] Inoue K, Nelson RA. The isolation and characterization of a new component of hemolytic complement, C'3e. J Immunol. 1965;96:355–67.

[27] Pillemer L, Blum L, Lepow IH, Ross OA, Todd EW, Wardlaw AC. The properdin system and immunity. I. Demonstration and isolation of a new serum protein, properdin and its role in immune phenomena. Science. 1954;120:279–85.

[28] Green H, Barrow P, Golberg B. Effect of antibody and complement on permeability control in ascites tumor cells and erythrocytes. J Exp Med. 1959;110:699–713.

[29] Borsos T, Dourmashkin RR, Humphrey JH. Lesions in erythrocyte membrane caused by immune hemolysis. Nature. 1964;202:251–2.

[30] Lachman PJ, Bowyer DE, Nicol P, Dawson RM, Munn EA. Studies on the terminal stage of complement lysis. Immunology. 1973;24:135–45.

[31] Haxby JA, Kinsky CB, Kinsky SC. Immune response of a liposomal model membrane. Proc Natl Acad Sci. 1968;61:300–7.

[32] Kinsky SC, Bonsen PP, Kinsky CD, Van Deenen LL, Rosenthal AF. Preparation of immunologically responsive liposomes with phosphoryl and phosphinyl analogs of lecithin. Biochim Biophys Acta. 1971;233:815–19.

[33] Mayer MM. Mechanism of cytolysis by complement. Proc Natl Acad Sci. 1972;69:2954–8.

[34] Tranum-Jensen J, Bhadki S, Bhakdi-Lehnen B, Bjerrum OJ, Speth V. Complement lysis; the ultrastructure and orientation of the C5b-9 complex on target sheep erythrocyte membranes. Scand J Immunol. 1978;7:45–6.

[35] Podack ER, Halverson C, Esser AF et al. SC5b-9 dimer: regeneration of the ability to interact with lipid by the selective removal of S-protein. J Immunol. 1977;120:492–8.

[36] Bieseker G, Podack ER, Halverson CA, Müller-Eberhard HJ. C5b-9 dimer: isolation from complement lysed cells and ultrastructural identification with complement dependent membrane lesions. J Exp Med. 1979;149:448–58.

[37] Bahkdi S, Bhadki-Lehnen B, Tranum-Jensen J. Proteolytic transformation of SC5b-9 into an amphiphilic macromolecule resembling the C5b-9 membrane attack complex of complement. Immunology. 1979;37:901–12.

[38] Podack ER, Tschopp J. Polymerization of the ninth component of complement (C9): formation of poly (C9) with a tubular structure resembling the membrane attack complex of complement. Proc Natl Acad Sci. 1982;79:574–8.

[39] Quincke H. Über akutes umschriebebes Hautodem. Monatsheefte für Praktische Dermatologie, 1882;1:129–31.

[40] Osler W. Hereditary angioneurotic angioedema. Am J Med Sci. 1888;95:362–7.

[41] Crowder JR, Crowder TR. Five generations of angioneurotic edema. Arch Intern Med 1917; 20: 840–852.

[42] Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. Am J Med. 1963;31:37–44.

[43] Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. Clin Immunol Immunopathol. 1972; 1:39.

[44] Landerman NS. Hereditary angioneurotic edema, I: case reports and review of the literature. J Allergy. 1962;33:316–29.

[45] Spaulding WB. Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). Ann Intern Med. 1960;53:739–45.

[46] Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. New Engl J Med. 1976;295:1444–8.

[47] Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. J Allergy Clin Immunol. 1980;65:75–9.

[48] Lundh B, Laurell AB, Wetterqvist H, White T, Granerus G. A case of hereditary angioneurotic oedema, successfully treated with ε-aminocaproic acid. Studies on C′1 esterase inhibitor, C′1 activation, plasminogen level and histamine metabolism. Clin Exp Immunol. 1968;3:733–45.

[49] Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. N Engl J Med. 1972;286:808–12.

[50] Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med. 1972;287:452–4.

[51] Brackertz D, Kueppers F. Possible therapy in hereditary angioneurotic edema (HAE). Klin Wschr 1973;51:620–2.

[52] Pickering RJ, Good RA, Kelly JR, Gewurz H. Replacement therapy in hereditary angioedema. Successful treatment of two patients with fresh frozen plasma. Lancet. 1969;1:326–30.

[53] Hill BJ, Thomas SH, McCabe C. Fresh frozen plasma for acute exacerbations of hereditary angioedema. Am J Emerg Med. 2004;22:633.

[54] Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med. 1996;20:1630–4.

[55] De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurised C1 inhibitor concentrate (Berinert® P) in hereditary angioedema: a review. Transfus Apher Sci. 2003; 29:247–54.

[56] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products of 19 December 1999. Official Journal L 018, 22/01/2000 P. 0001-0005.

[57] Bock SC, Skriver K, Nielsen E, Thogersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. Biochemistry. 1986;25:4292–301.

[58] Davis AE III, Whitehead AS, Harrison RA, Dauphinais A, Bruns GA, Cicardi M, et al. Human inhibitor of the first component of complement, C1: characterization of cDNA clones and localization of the gene to chromosome 11. Proc Natl Acad Sci USA. 1986;83:3161–5.

[59] Tosi M, Duponchel C, Bourgarel P, Colomb M, Meo T. Molecular cloning of human C1 inhibitor: sequence homologies with alpha 1-antitripsin and other members of the serpins superfamily. Gene. 1986;42:265–72.

[60] Warin RP, Cunliffe WJ, Greaves MW, Wallington TB. Recurrent angioedema: familial and oestrogen-induced. Br J Dermatol. 1986;115:731–4.

[61] Binkley K, Davis A 3rd. Clinical, biochemical and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol. 2000; 106;546–50.

[62] Börk K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet. 2000;356:213–7.

[63] Dewald G, Börk K. Missense mutations in the coagulation factor XII (Hageman Factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Communs. 2006;343:1286–9.

[64] Cichon S, Martin L, Hennies HC, Muller F, Van Driessche K, Karpushova A, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet. 2006;79:1098–104.

[65] Martin L, Raiso-Peyron N, Nothen M, Cichon S, Drouet C. Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. J Allergy Clin Immunol. 2007;120;975–7.

[66] Strang CJ, Cholin S, Spragg J, Davis AE 3rd, Schneeberger EE, Donaldson VH, et al. Angioedema induced by a peptide derived from complement component C2. J Exp Med. 1988;168:1685–98.

[67] Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angioedema. Lancet. 1998;351:1693–7.

[68] Davis AE. The pathogenesis of hereditary angioedema. Transfus Apheresis Sci. 2003; 29:195–203.

[69] Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. J Clin Invest. 2002;109:1057–63.

[70] Bas M, Bier H, Greve J, Kojda G, Hoffmann TK. Novel pharmacotherapy of acute hereditary angioedema with bradykinin B2-receptor antagonist Icatibant. Allergy. 2006; 61:1490–2.

[71] Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). J Allergy Clin Immunol. 2007; 119: 1497–503.

[72] European Medicines Agency. European Public Assessment Report (EPAR) for Firazyr [updated 01.12.11; accessed 11.01.17]. Available from: http://www.ema.europa.eu/

[73] FDA Cinryze® Approval Letter. Accessed 11.01.07. Available from: http://www.fda.gov/

[74] Burnouf T, Radosevich M. Nanofiltration of plasma-derived biopharmaceutical products. Haemophilia. 2003;9:24–37.

[75] World Health Organization. Annex 4 Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. WHO Technical Report. 2004;924 Series No.

[76] Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363:513–22.

[77] Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitorin hereditary angioedema. Am J Med. 2012;125:938.e1–7.31.

[78] European Medicines Agency. European Public Assessment Report (EPAR) for Cinryze [updated 23.11.16; accessed 11.01.17]. Available from: http://www.ema.europa.eu/

[79] European Medicines Agency. European Public Assessment Report (EPAR) for Berinert [accessed 11.01.17]. Available from: http://www.ema.europa.eu/

[80] FDA Berinert® Approval Letter. Accessed 11.01.07. Available from: http://www.fda.gov/

[81] FDA Kalbitor® Approval Letter. Accessed 11.01.07. Available from: http://www.fda.gov/

[82] Choi G, Soeters M, Farkas H, Varga L, Obtulowitz K, Bilo B, et al. Recombinant human C1-inhibitor in the treatment of acute angioedema attacks. Transfusion. 2007;47:1028–32.

[83] European Medicines Agency. European Public Assessment Report (EPAR) for Ruconest [updated 24.05.16; accessed 11.01.17]. Available from: http://www.ema.europa.eu/

[84] FDA Ruconest® Approval Letter. Accessed 11.01.07. Available from: http://www.fda.gov/

[85] Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase Inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114:S51–131.

[86] Levi M, Choi G, Picavet C, Hack E. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. J Allergy Clin Immunol. 2006;117:904–8.

[87] Longhurst H, Buckland M, O'Grady C. Home therapy for hereditary angioedema: the Barts experience. C1-Esterase Inhibitor Deficiency Workshop. Budapest. 16–18 May 2003. Abstracts Book. 39–40.

[88] Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol. 2009, 19:147–51.

[89] Cicardi M, Craig TJ, Martinez-Saguer I, Hébert J, Longhurst HJ. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration. Int Arch Allergy Immunol. 2013;161(Suppl 1):3–9.

[90] Caballero T, Sala-Cunill A, Cancian M, Craig TJ, Neri S, Keith PK et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. Int Arch Allergy Immunol. 2013;161(Suppl 1):10–6.

[91] Bork K. Hereditary angioedema with normal C1 inhibitor. Immunol Allergy Clin North Am. 2013;33:457–70.

[92] Binkley K, Davis A 3rd. Clinical, biochemical and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol. 2000;106;546–50.

[93] Börk K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet. 2000;356:213–7.

[94] Marcos C, López Trascasa M, Luna I, González R. Another type of angioedema relative: angioedema induced oestrogen. (Otro tipo de angioedema familiar: angioedema estrógeno-inducido). Rev Esp Alergol Inmunol Clin 2000. XXII Congress of the Spanish Society of Allergology and Clinical Immunology (SEAIC). Pamplona, 16–19 Sept 2000.

[95] Marcos C, López-Lera A, Varela S, Liñares T, Álvarez-Eire MG, López-Trascasa M.Clinical, biochemical and genetic characterization of type III hereditary angioedema in 13 Northwest Spanish families. Ann Allergy Asthma Immunol. 2012; 109:195–200.

[96] Martin L, Degenene D, Toutain A, Ponard D, Watier H. Hereditary angioedema type III: an additional French pedigree with autosomal dominant transmission. J Allergy Clin Immunol. 2001;107:747–8.

[97] Boulliet L, Ponard D, Drouet C, Jullien D, Massot C. Angioedema and oral contraception. Dermatology. 2003;206:106–9.

[98] Dewald G, Börk K. Missense mutations in the coagulation factor XII (Hageman Factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun. 2006;343:1286–9.

[99] Cichon S, Martin L, Hennies HC, Muller F, Van Driessche K, Karpushova A, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet. 2006;79:1098–104.

[100] Martin L, Raiso-Peyron N, Nothen M, Cichon S, Drouet C. Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. J Allergy Clin Immunol. 2007;120;975–7.

[101] Börk K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. J Allergy Clin Immunol. 2009;124:129–34.

[102] Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. Allergy. 2015;70:1004–12.

[103] de Maat S, Björkqvist J, Suffritti C, Wiesenekker CP, Nagtegaal W, Koekman A, et al. Plasmin is a natural trigger for bradykinin production in patients with hereditary angioedema with factor XII mutations. J Allergy Clin Immunol. 2016;138:1414–23.

[104] Serrano C, Guilarte M, Tella R, Dalmau G, Bartra J, Gaig P, et al. Estrogen-dependent hereditary angio-oedema with normal C1 inhibitor: description of six new cases and review of pathogenic mechanisms and treatment. Allergy. 2008;63:735–41.

[105] Prieto A, Tornero P, Rubio M, Fernandez-Cruz E, Rodriguez-Sainz C. Missense mutation Thr309Lys in the coagulation factor XII gene in a Spanish family with hereditary angioedema type III. Allergy. 2009;64:284–6.

[106] Baeza ML, Rodríguez-Marco A, Prieto A, Rodríguez-Sainz C, Zubeldia JM, Rubio M. Factor XII gene missense mutation Thr328Lys in an Arab family with hereditary angioedema type III. Allergy. 2011;66:981–2.

[107] Gómez-Traseira C, López-Lera A, Drouet C, López-Trascasa M, Pérez-Fernández E, Favier B, et al. Hereditary angioedema caused by the p.Thr309Lys mutation in the F12 gene: a multifactorial disease. J Allergy Clin Immunol. 2013;132:986–9.e1-5.

[108] Piñero-Saavedra M, González-Quevedo T, Saenz de San Pedro B, Alcaraz C, Bobadilla-González P, Fernández-Vieira L, et al. Hereditary angioedema with F12 mutation: Clinical features and enzyme polymorphisms in 9 Southwestern Spanish families. Ann Allergy Asthma Immunol. 2016;117:520–526.

[109] Vitrat-Hincky V, Gompel A, Dumestre-Perard C, Boccon-Gibod I, Drouet C, Cesbron JY, et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. Allergy 2010;65:1331–6.

[110] Duan QL, Binkley K, Rouleau GA. Genetic analysis of factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. J Allergy Clin Immunol. 2009;123:906–10.

[111] Börk K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1I inhibitor. Clin Immunol. 2011;141:31–5.

[112] Kiss N, Barabás E, Várnai K, Halász A, Varga LÁ, Prohászka Z et al. Novel duplication in the F12 gene in a patient with recurrent angioedema. Clin Immunol. 2013;149:142–5.

[113] Grumach AS, Stieber C, Veronez CL, Cagini N, Constantino-Silva RN, Cordeiro E, et al. Homozygosity for a factor XII mutation in one female and one male patient with hereditary angio-oedema. Allergy. 2016;71:119–23.

[114] Börk K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. Allergy Asthma Clin Immunol. 2010;6:15.

[115] Bouillet L, Boccon-Gibod I, Ponard D, Drouet C, Cesbron JY, Dumestre-Perard C, et al. Bradykinin receptor 2 antagonist (Icatibant) for hereditary angioedema type III attacks. Ann Allergy Asthma Immunol. 2009;103:448.

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