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Review

The autoimmune side of hereditary angioedema: insights on the pathogenesis

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ABSTRACT

Hereditary angioedema (HAE) is an autosomal dominant disease resulting from the deficiency of C1 inhibitor (C1-INH), a glycosylated serine protease inhibitor that plays a regulatory role in the complement system (CS), the contact system and the intrinsic coagulation cascade. HAE disease severity is highly variable and may be influenced by genetic polymorphisms as well as by other factors, such as gender hormone-mediated effects. In HAE, the potential inadequate clearance of immune-complexes (IC) in the presence of reduced levels of CS components and in turn an excess of IC in the tissues results in inflammatory damage and release of autoantigens that may trigger an autoimmune response. Occasional reports link HAE with autoimmune conditions and only few studies have been conducted on large patient populations with controversial results. Although several immunoregulatory disorders have been documented, the prevalence of defined autoimmune diseases in patients with HAE remains debated. The occurrence of autoimmune conditions in HAE patients may worsen the disease severity enhancing the complexity of the comprehensive care.

Contents

1. Introduction

Hereditary angioedema (HAE; Online Mendelian Inheritance in Man OMIM# 106100) is a rare autosomal dominant disorder that is defined by a deficiency of the first component of complement (C1) esterase inhibitor (Cl-INH), a glycosylated serine protease inhibitor that plays a regulatory role in the complement system (CS), the contact system and the intrinsic coagulation cascade [1–3]. The gene encoding the C1-INH (SERPING1; OMIM# 606860) has been mapped on the chromosome 11q12–13.1 [1,3]. Several mutations through the gene are responsible for the type I HAE that is characterized by a deficiency of the synthesis of the C1-INH while mutations in specific areas of the gene are responsible for the type II HAE, which is characterized by the synthesis of a dysfunctional protein [1,3]. Type III HAE is a form of HAE not associated with C1-INH deficiency or dysfunction. It is found predominantly in women and may be due to known mutations in the factor XII gene (F12) or to unknown genetic mutations [4]. Approximately 25% of European patients with HAE with normal C1-INH have been identified as having a mutation of the gene F12 (chromosome

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5q35.3), but the functional consequences of F12 mutations remain unknown [5]. HAE related to C1-INH deficiency occurs in about 2% of all the clinical angioedema. Because of its rarity (1 in 50,000 individuals affected, range: 1 in 10,000–1:150,000 worldwide) there is often a long delay between the onset of symptoms and the diagnosis [6]. Type I HAE is the most frequent: 85% of patients show decreased C1-INH antigenic and functional levels while 15% show normal or increased concentrations of a dysfunctional C1-INH protein (type II HAE). Quincke's denomination of the disease in 1882 as "angioneurotic" reflects the patients' experience as a main triggering event: mental stress [7]. Both emotional and physical stresses appear to activate fibrinolysis [7]. Clinical manifestations of C1-INH deficiency are a result of increased vascular permeability in subcutaneous and submucosal soft tissues including recurrent episodes of non-pitting edema of the extremities, face, upper respiratory tract, gastro-intestinal mucosa and genitals, with a variety of clinical complications and management issues [3]. The edema develops slowly over a period of up to 36 hours and resolves 1 to 3 days later [3]. Several studies emphasize that symptoms of HAE manifest in a variety of ways, and therefore, could be confused with those of other disorders. Moreover, it is clearly demonstrated the wide variation in frequency and severity of symptoms, even in the same patient at different phases of life. HAE diagnosis is performed by taking into account the genealogic studies showing the autosomal dominant pattern of inheritance as well as the clinical characteristics of the acute episodes, and requires laboratory evaluation with a confirmation of C1-INH deficiency by means of immunochemical and functional assays [1]. A large spectrum of mutations has been described in the C1-INH gene, that can lead to a failure in both secretion and production of C1-INH protein [3]. At present, over 200 different mutations have been identified and about 25% of them resulted from de novo mutations. Several mutation-scanning methods have been applied to the detection of sequence variation in the C1-INH gene. We previously reported the efficacy of the Denaturing High Performance Liquid Chromatography (DHPLC) in detecting C1-INH mutations and polymorphisms and its advantages in terms of time, cost, and complexity compared with direct DNA sequence analysis [8,9]. Treatment of HAE consists of management of acute attacks, and short-term and long-term prophylaxes [10,11]. It is recommended in treating acute HAE attacks as early as possible by using plasma-derived C1-INH or recombinant C1-INH as well as the bradykinin receptor blocker [10–12]. The kallikrein inhibitor is approved for the treatment of HAE in the USA but not in Europe [10]. Attenuate androgens, antifibrinolytics, and plasma-derived C1-INH are indicated for the short-term and long-term prophylaxes [10].

2. Complement system and autoimmunity

The CS is a major component of the immune response and the host defense to infection bridging the innate immunity with the adaptive immunity. The key point of the activation of the CS is the formation of the C3-convertase that leads to the formation of the C3b and the C3a fragments. The C3b is an opsonin that is important to opsonization and phagocytosis [13]. C3a together with C5a are anaphylatoxins that trigger other immune reactions in the context of the immune response. The activation of the final complement components and the formation of the membrane attack complex (MAC) lead to cell injury. C3b results from the activations of each of the three CS pathways: classical, alternative, and lectin pathways [13]. C1-INH also targets proteins associated with the intrinsic coagulation cascade (such as thrombin, plasmin, tissue plasminogen activator — tPA) and the contact system (such as the factor XII and the plasma kallikrein) [3]. The alteration of the C1-INH-mediated regulation results in an interference with those systems and with the interactions among them. The main effect consists of the overproduction and the accumulation of the bradykinin, that is a potent vasoactive peptide that is able to cause vasodilatation, to increase vascular permeability, to produce hypotension and constrict uterine and gastro-intestinal smooth muscles [3]. The relationship between the CS and autoimmunity is apparently paradoxical. On one hand, CS activation contributes to tissue damage in autoimmune diseases, whereas on the other hand, deficiency of complement proteins leads to autoimmunity [13]. Several theories have been proposed to explain the association between deficiencies of the CS components and autoimmune diseases. The inadequate clearance of immune-complexes (IC) in the presence of reduced levels of CS components and an excess of IC in the tissues result in inflammatory damage and release of autoantigens that trigger an autoimmune response [13,14]. Furthermore, the presence of high concentration of apoptotic cells due to poor clearance may elicit an autoimmune response [15]. In particular, among complement proteins, a primary role in clearance activity is attributed to the first component of the complement C1q [16]. Several reports describe patients presenting angioedema attacks identical to that seen in HAE and exhibiting low or undetectable CH50, C2, C4, and, frequently, decreased C1q, in addition to low levels of C1-INH commonly in association with lymphoproliferative and/or autoimmune disorders [17,18]. This syndrome is defined as acquired angioedema (AAE type I) and it is observed often in association with other diseases. A second form of AAE (type II) was documented in 1986 and was found to be mediated by an IgG autoantibody against C1-INH [19]. The majority of the paraproteins in AAE type I are frequently circulating autoantibodies to C1-INH usually encountered in AAE type II, suggesting that the distinction between type I and type II AAE may be artificial [17]. Moreover, lymphoproliferation and autoimmunity coexist in most patients and might also develop one from the other [20]. Monoclonal gammopathy of undetermined significance (MGUS) is the most frequent condition associated with the acquired C1-INH deficiency [21]. Autoantibodies anti-C1-INH seem to prevent the inhibitory activity of the C1-INH on target proteases and convert the inhibitor into a substrate that can be cleaved to an inactive form. Although lymphoproliferative diseases represent the main group encountered in AAE and a direct pathogenetic relationship between the two conditions has been described, systemic lupus erythematosus (SLE), infections and neoplasias have also been observed in association with AAE [20,22]. In a multicenter study, it has been described that SLE patients showed higher anti-C1-INH level than the healthy controls and furthermore, the anti-C1-INH levels correlate with duration and activity of the disease but not with organ manifestations [23]. In the serum of patients with autoimmune diseases, mainly SLE and hypocomplementemic urticarial vasculitis syndrome, autoantibodies directed to C1q, which recognize the collagen-like region of C1q molecule, are well reported and contribute to clinical manifestations in those conditions [16,24]. Although autoantibodies against C1-INH and C1q can occur in a variety of conditions, the possibility chance association for some of these conditions cannot be completely ruled out [16,22].

3. HAE and autoimmunity: the interplay between genes and hormones

Complex diseases encompass a mosaic of immune dysregulation, genetic susceptibility, and hormonal and environmental factors [25]. HAE disease severity is highly variable and may be influenced by polymorphisms in other genes different from the SERPING1 and the F12 as well as by other factors, such as hormones, trauma, stress, and infections [26]. Regulation of the bradykinin B2 receptor and peptidases that degrade bradykinin may influence HAE disease severity [26]. It is well documented that the role of bradykinin-forming pathways and their interrelationships with CS as a major contributor to the innate inflammatory response supporting the pathogenic mechanisms of the bradykinin mediated disease [27]. In this context, genetic background may affect the clinical outcome of HAE patients. Complements C2 and C4 are HLA encoded components and their link with other HLA disease susceptibility genes may explain the association between complement deficiencies – including HAE – and diseases driven by IC [28]. However, C1-INH deficiency in HAE does not seem to be linked with HLA, and there is