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The role of the complement system in hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare, but potentially life-threatening disorder, characterized by acute, recurring, and self-limiting edematous episodes of the face, extremities, trunk, genitals, upper airways, or the gastrointestinal tract. HAE may be caused by the deficiency of C1-inhibitor (C1-INH-HAE) but another type of the disease, hereditary angioedema with normal C1-INH function (nC1-INH-HAE) was also described. The patient population is quite heterogeneous as regards the location, frequency, and severity of edematous attacks, presenting large intra- and inter-individual variation. Here, we review the role of the complement system in the pathomechanism of HAE and also present an overview on the complement parameters having an importance in the diagnosis or in predicting the severity of HAE.

1. Introduction

Hereditary angioedema (HAE) is a rare disorder, which belongs to the group of bradykinin-mediated angioedemas. Clinically, it is characterized by the unpredictable occurrence of recurrent, non-pruritic, and self-limiting angioedema without wheals. Edema develops in the subcutaneous and/or submucosal tissues, and does not respond to standard treatment with antihistamines, glucocorticosteroids, and epinephrine (Agostoni et al., 2004; Zuraw, 2008; Longhurst and Cicardi, 2012). HAE attacks may involve the extremities, the face, the trunk, and the genitals. In the gastrointestinal tract, angioedema may mimic an abdominal catastrophe, whereas in the upper airways, it may cause obstruction leading to suffocation (Bork et al., 2006). The clinical manifestations exhibit intra- and inter-individual variation. Two main types of HAE can be distinguished: hereditary angioedema with C1-inhibitor (C1-INH) deficiency (C1-INH-HAE) and hereditary angioedema with normal C1-INH function (nC1-INH-HAE) (Cicardi et al., 2014). The considerations as regards the diagnosis of HAE and how to predict the disease severity are briefly summarized in Fig. 1.

1.1. Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE)

The genetic defect of the *SERPING1* gene results in a biochemical abnormality of the serpin-type protease inhibitor, C1-INH. In C1-INH-HAE type I, the C1-INH protein is produced in smaller quantities, whereas in C1-INH-HAE type II, the secreted protein is dysfunctional (Rosen et al., 1965). C1-INH regulates the complement, contact, coagulation, and fibrinolytic plasma enzyme cascades. The deficiency of C1-INH leads to the uncontrolled, spontaneous activation of C1, and to the consumption of C4 and C2. The decreased functional activity of C1-INH may result in activation of the contact system on endothelial surfaces; this is initiated by coagulation factor XII (FXII), which undergoes autoactivation to factor XIIa. This active protease triggers further activation of FXII to FXIIa; the latter converts prekallikrein into plasma kallikrein. Kallikrein cleaves bradykinin from high-molecular-weight kininogen (HMWK). Bradykinin then binds to and activates the bradykinin B2 receptor (constitutively present on the surface of endothelial cells), causing vasodilation, increased vascular permeability, and plasma leakage into the extracellular space, leading to edema formation (Nussberger et al., 1999; Kaplan and Joseph, 2010; Cugno et al., 2003). *De novo*-produced bradykinin is active for a short time only, because a number of kininases, such as neural endopeptidase or neprilysin, dipeptidyl peptidase IV, aminopeptidase P, and angiotensin-converting enzyme (ACE) break down bradykinin to inactive peptides. The diagnosis can be established based on clinical symptoms, family history, and complement parameters. In 75% of the cases, angioedematous episodes occur also in other members of the family. Males and females are affected in equal proportions (50:50%). The complement profile is characterized by normal C1q and decreased C4 levels, as well as by the lower functional activity of C1-INH. Furthermore, C1-INH concentration is lower in type I C1-INH-HAE, whereas it is normal or elevated in type II C1-INH-HAE (Table 1). When the complement screen is inconclusive, genetic testing may prove useful for early diagnosis in C1-INH deficient neonates, as well as in preimplantation or in prenatal diagnostics (Farkas et al., 2017; Caballero et al., 2012).

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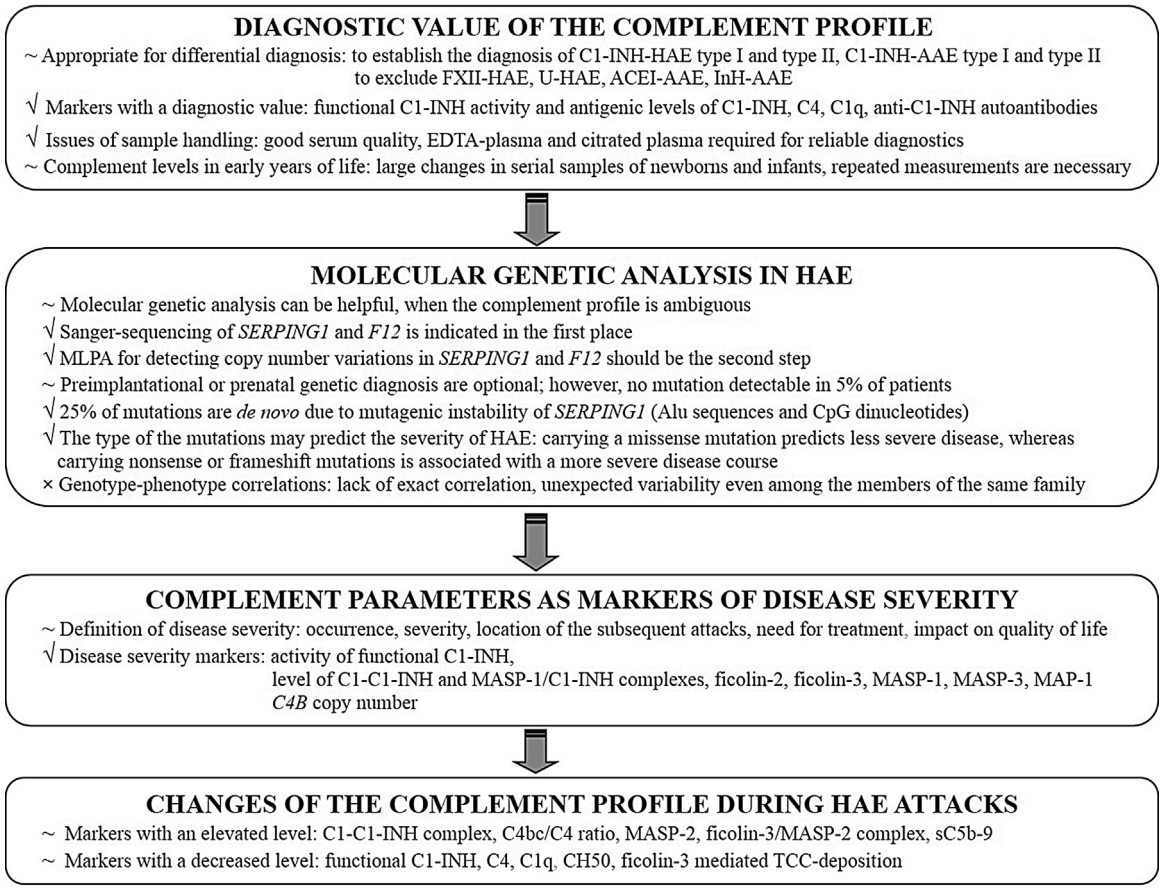

Fig. 1. √: accepted, proven statement. ~: less exact statement. ×: no proven relationship.

1.2. Hereditary angioedema with normal C1-INH function (nC1-INH-HAE)

In addition to the recurrence of HAE attacks, to the ineffectiveness of standard therapy, and to the positive family history, this form of HAE is characterized by a greater proportion of affected females, and by a normal complement screen (Bork et al., 2007). Complement testing should be performed to exclude C1-INH deficiency. There is no laboratory method for the specific diagnosis of nC1-INH-HAE. The etiology of this disease is unknown in a large proportion of cases (U-HAE). In the remaining 25–30%, a mutation with incomplete penetrance can be detected in the gene of factor XII (FXII-HAE) (Table 1) (Bork et al., 2015). These “gain of function” mutations result in the increased functional (amidolytic) activity of factor XII (Cichon et al., 2006). Further, these mutations alter FXII glycosylation, and this leads to the increased autoactivation of FXII (Bjorkqvist et al., 2015). Finally, the mutations create new sites susceptible to enzymatic cleavage by plasmin. FXIIa levels are significantly higher after plasmin cleavage in FXII mutants, and the latter may escape inhibition by the C1-inhibitor (de Maat et al., 2016). These processes may lead to the activation of the contact system, as well as to bradykinin release. The factor XII gene (*F12*) is under positive regulation by estrogens, which explains why this disease form is much more common in females (Bork, 2013).

2. Differential diagnosis of angioedemas

Possible differential diagnostic options include acquired, bradykinin-mediated angioedemas, as their clinical manifestations and response to standard therapy are identical to those seen in hereditary angioedemas (Cicardi et al., 2014; Craig et al., 2014; Bernstein et al., 2017). In addition to a negative family history, the following may assist in establishing the diagnosis: symptom onset later in life, and treatment with angiotensin-converting enzyme inhibitors (in some subtypes), as well as the recognition of certain underlying disorders (Farkas et al., 2016a). In acquired C1-inhibitor deficiency, the decrease of C4 levels, as well as of C1-INH concentration and functional activity are accompanied by a low C1q level (C1-INH-AAE); moreover, antibodies against C1-INH can be detected in a proportion of cases. Underlying diseases, lymphoproliferative diseases in particular, can lead to complement activation and the absorption or consumption of C1-INH. Antibodies against C1-INH may inactivate C1-INH and it may be more prone to

Table 1
The laboratory diagnosis of hereditary angioedema.

Type of HAE	C1-INH functional activity	C1-INH concentration	C4	C1q	Anti-C1-INH antibody	Total activity of the classical pathway	Mutation in the *SERPING1* gene	Mutation in the *F12* gene
C1-INH-HAE type I	Low	Low	Low	Normal	No	Low	Yes	No
C1-INH-HAE type II	Low	Normal/Low	Low	Normal	No	Low	Yes	No
FXII-HAE	Normal	Normal	Normal	Normal	No	Normal	No	Yes
U-HAE	Normal	Normal	Normal	Normal	No	Normal	No	No