Hereditary Angioedema and Autoimmunity

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Hereditary angioedema (HAE) is a rare autosomal dominant disorder that is defined by a deficiency of complement component 1 (C1) esterase inhibitor (Cl-INH), a glycosylated serine protease inhibitor (serpin) that plays a regulatory role in the complement cascade, the contact system, and the intrinsic coagulation cascade [1]. Deficiency of this regulator causes chronic activation of the complement cascade with a resultant deficiency of C4 and C2 and the overproduction of bradykinin, leading to increased vascular permeability and severe edema [1].

HAE accounts for approximately 2% of clinical angioedema cases and affects approximately 1 in 50,000 people. HAE is due to mutations in the C1-INH gene (*SERPING1*) that result in deficiency or functional impairment of C1-INH. The most common is type I (85% of all HAE), which is related to a mutation of one copy of the *SERPING1* gene and is characterized by low levels of both C1-INH antigen and functional activity. HAE type II (15%–20% of all HAE) is clinically indistinguishable from type I and is characterized by mutations of the *SERPING1* gene, leading to the production of non-functional enzyme with normal or even high levels of low functional C1-INH antigen. HAE type III is a form of HAE not caused by C1-INH deficiency or dysfunction with normal C1-INH; it is found predominantly in women and may be due to known mutations in the factor XII gene or to unknown genetic mutations [1].

Data from the literature on HAE prevalence were recently confirmed in a report by the Italian Network for C1-INH-HAE (ITACA), established in 2012, in which our Division represents one of the 17 active centers. The ITACA database included 983 patients (53% female) with C1-INH-HAE from 376 unrelated families: the minimal prevalence of C1-INH-HAE in Italy in 2013 was 1.54:100,000 inhabitants, equivalent to a prevalence of 1:64,935 (median age of patients 45 years, with median age at diagnosis 26 years). The majority of patients (87%) had C1-INH-HAE type I; patients with type II comprised 13%. Clinical manifestations of C1-INH deficiency are a result of increased vascular permeability in subcutaneous and submucosal soft tissues and include recurrent episodes of non-pitting edema of the extremities, face, upper respiratory tract, gastrointestinal mucosa and genitals, with a variety of clinical complications and management issues [1]. The edema develops slowly over a period of up to 36 hours and resolves 1 to 3 days later. C1-INH deficiency may be also acquired. Angioedema due to acquired C1-INH deficiency, frequently referred to as acquired angioedema (AAE), has been reported rarely, usually in association with lymphoproliferative disorders or autoimmune, neoplastic, or infectious diseases [2]. The disease generally manifests in adulthood and is characterized by decreased activity of C1-INH, decreased but sometimes normal levels of C1-INH protein, decreased C4 and, frequently, decreased C1q.

Autoantibodies to 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. Autoantibodies directed to C1-INH were also identified in patients without diseases, suggesting the existence of two forms of acquired C1-INH deficiency: type 1 associated with B cell disorders and type 2 with autoantibodies. This issue was later questioned and it is now clear that patients with C1-INH autoantibodies may have or may develop B cell malignancies. Monoclonal gammopathy of unknown significance (MGUS) is the most frequent condition associated with the acquired C1-INH deficiency [2]. In the context of the autoimmune mechanisms involving the complement components, autoantibodies directed to C1q, which recognize the collagen-like region (CLR) of C1q molecule, are frequently present in the serum of patients with autoimmune diseases, mainly systemic lupus erythematosus (SLE) and hypocomplementemic urticarial vasculitis syndrome, contributing to clinical manifestations in those conditions [3]. Several investigators have demonstrated the presence of anti-C1q autoantibodies in sera of patients with rheumatoid arthritis, in patients with renal diseases as well as in healthy individuals [3].

Advances in our understanding of immunologic pathways in the complement system provide new insights on the immunoregulatory disorders as well as the autoimmune manifestations in HAE patients [4]. Occasional reports have linked HAE with autoimmune diseases and only a few studies have been conducted on large patient populations, with controversial results. In 1986, Brickman et al. [5] systematically evaluated 157 patients with HAE-C1-INH for manifestations of autoim-

munity and reported an increased frequency of autoimmune disease. In 1987, Muhlemann et al. [6] screened 91 patients with HAE-C1-INH for thyroid antibodies and found that the prevalence of thyroglobulin antibodies and thyroid peroxidase in the group of young female patients with HAE-C1-INH was higher than expected. A low frequency of autoimmune disease was found by Agostoni and Cicardi [7], who identified only one case of rheumatoid arthritis and a single case of Sjögren's syndrome (SjS) among 226 HAE-C1-INH patients. In 1996, Nielsen et al. [8] revealed no statistically significant differences between HAE-C1-INH patients and their healthy relatives concerning the prevalence of autoantibodies, although rheumatic complaints were reported by 53% of HAE-C1-INH patients and 12% of their unaffected relatives [8]. Farkas et al. analyzed clinical data and immunoserologic parameters of 130 HAE-C1-INH and 174 non-C1-INH-deficient patients with angioedema, but did not find a higher prevalence of immunoregulatory disorders among HAE-C1-INH patients [9]. Interestingly, immunoserology screening revealed a greater prevalence of anticardiolipin IgM among HAE-C1-INH patients than in those with non-C1-INH-deficient angioedema [9].

To advance our understanding of immunoregulatory disorders in HAE patients, we recently performed a large population study in HAE patients in collaboration with the Allergy and Clinical Immunology Units at medical centers in Israel [10]. We characterized the profile of autoantibodies in a group of HAE patients in terms of rheumatoid factor, antinuclear autoantibodies, anticardiolipin, anti-tissue transglutaminase, anti-endomysial, anti-*Saccharomyces cerevisiae*, anti-thyroid and anti-neutrophil cytoplasmic antibodies. We also analyzed the memory B cell phenotype, the Toll-like receptor (TLR)-9 expression and total phosphotyrosine in B cells isolated from HAE patients. We demonstrated that HAE patients have enhanced production of autoantibodies due most probably to the increased activation of B cells, which was found to be associated with a high expression of TLR-9.

According to our database, which collects medical histories and laboratory findings of HAE patients referred to our Division, we systematically reviewed the medical records of 143 patients with HAE for manifestations of autoimmunity. Characteristics of those 143 patients are as follows: 72 women [65/72 (90.3%) type I HAE; 7/72 (9.7%) type II HAE; mean age at diagnosis 28.13 ± 18.7 years] and 71 men [61/71 (86%) type I HAE; 10/71 (14%) type II HAE; mean age at diagnosis 27 ± 17.7 years]. Among these patients, we diagnosed autoimmune diseases in 6 (4.2%): antiphospholipid syndrome in 2 patients with type I HAE, systemic sclerosis in a man with type II HAE, psoriatic arthritis in a man with type I HAE, SLE in a woman with type I HAE, and mixed connective tissue disease in a man with type I HAE. It should be noted that most of the patients with autoimmune conditions were affected by type I HAE and that for all these patients a familial history for HAE was registered. Interestingly, the range of time between the HAE diagnosis and the detection of the autoimmune conditions was wide (9–30 years). We reported also a diagnosis of SjS in a woman with AAE whose complement component serum levels at the time of the medical evaluation were lower than normal values, as were the levels of C1-INH (both C1-INH antigen and functional activity). In addition, anti-C1-INH autoantibodies (IgG, IgM and IgA) were not detected but a mild positivity for serum anti-CLR/C1q autoantibodies was noted. Interestingly, in this case, the time from the appearance of angioedema signs to the autoimmune manifestations was short. Thus, AAE appeared to be dependent on complement consumption and/or formation of immune complexes in the context of the autoimmune disorder. Characteristics of all the above mentioned patients are described in Table 1.

Table 1. Characteristics of patients with angioedema and autoimmune diseases referred to our Division

Patient	Type of AE	Gender	Age at AE diagnosis (yr)	Autoimmune disease	AE disease duration* (yr)
1	Type I HAE	M	29	APS	9
2	Type I HAE	F	29	APS	9
3	Type II HAE	M	20	SSc	22
4	Type I HAE	M	51	PsA	10
5	Type I HAE	F	6	SLE	29
6	Type I HAE	M	27	MCTD	30
7	AAE	F	45	SjS	1

*AE disease duration at the time of the autoimmune disease diagnosis

HAE = hereditary angioedema, AE = angioedema, AAE = acquired angioedema, APS = antiphospholipid syndrome, SSc = systemic sclerosis, PsA = psoriatic arthritis, SLE = systemic lupus erythematosus, MCTD = mixed connective tissue disease, SjS = Sjögren syndrome

Further investigations are needed to explore the immunologic pathways as well as the clinical features of the autoimmune manifestations in HAE patients. New insights on the autoimmune mechanisms involving the complement components could reduce the delay in both reaching a diagnosis and detecting an autoimmune complication, thereby improving the clinical and pharmacological management of HAE patients.

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