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Clinical and scientific letters

OVERVIEW

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Hereditary angioedema with F12 mutation: first report of three cases associated with immune disorders.

Hereditary angioedema (HAE) is a rare genetic disorder that is characterised by recurrent subcutaneous oedema, abdominal pain and laryngeal oedema, the last of which is life threatening if not treated. There are two distinct types of HAE. The first type is related to the C1 inhibitor (HAE-C1-INH) and is in turn subclassified into type 1, with deficits of C1-INH production, and type 2 with production of a dysfunctional C1-INH. In the second type of HAE, C1-INH concentrations and activity are normal, but about 25% of cases are associated with a mutation in the *F12* gene, which encodes for Hageman factor (HAE-FXII).[1]

Associations with other immune disorders, mainly lupus, have been described in HAE-C1-INH, [2–4] but not in HAE-FXII. We present three cases of HAE-FXII associated with other immune disorders – three women with hormonal triggered symptoms and normal C3 and C4. Analysis of their *F12* genes revealed a Thr328Lys missense mutation.

The first patient developed symptoms of HAE (swelling of the face and limbs, abdominal pain) when she was 17 years old. HAE-FXII was diagnosed 10 years later. A year after that, she developed clinically and histologically confirmed morphea. Immunological investigations revealed antinuclear factors at 1/160 and double-stranded DNA antibodies at 13 IU (normally <5 IU). Neither Scl70 antibodies nor symptoms of systemic sclerosis were noted. No one else in her family had symptomatic HAE.

The second patient had symptoms of HAE since the age of 21, when she started taking oral oestroprogestative contraception. She was diagnosed with HAE-FXII two years later. She developed urticarial rash at age 27 years. Histological examination of the skin revealed leucocytoclastic vasculitis. Her blood C3 and C4 concentrations were normal. She underwent treatment with dapsone for urticarial vasculitis and experienced several relapses.

The third patient developed symptoms of HAE at age 18 years after using an oral contraceptive. HAE-FXII was diagnosed 10 years later, and that same year she developed lung sarcoidosis with hilar lymphadenopathy, reticulonodular infiltrates and elevated level of angiotensin-converting enzyme. Sarcoidosis regressed spontaneously.

Although association between HAE-C1-INH and immune disorders had previously been reported, this is the first description of HAE-FXII patients with other immune disorders. Furthermore, neither sarcoidosis nor morphea had been reported in patients with HAE before.

We cannot assess in this first report whether the association of HAE-FXII with other immune disorders is fortuitous or not. We believe nevertheless that clinicians should be made aware of the potential link. If such a relation exists, its pathophysiology probably differs from that of HAE–C1-INH, where the modulation of the classical complement pathway is thought to be involved[2,5]. ■

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References

1 Bork 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.
2 Brickman CM, Tsokos GC, James E *et al.* Immunoregulatory disorders associated with hereditary angioedema. *I. Clinical manifestations of autoimmune disease. J Allergy Clin Immunol* 1986;77:749–57.
3 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206–15.
4 Farkas H, Csuka D, Gács J *et al.* Lack of increased prevalence of immunoregulatory disorders in hereditary angioedema due to C1-inhibitor deficiency. *Clin Immunol* 2011;141:58–66.
5 Lipsker D, Hauptmann G. Cutaneous manifestations of complement deficiencies. *Lupus* 2010;19:1096–106.