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Review

Hereditary angioedema and lupus: A French retrospective study and literature review

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disorder that is primarily caused by a defect in the C1 inhibitor (C1-INH). The recurrent symptoms are subcutaneous edema and abdominal pain. Laryngeal edema, which can also occur, is life threatening if it goes untreated. HAE can be associated with some inflammatory and autoimmune disorders, particularly lupus. The aim of this study was to describe cases of lupus among HAE patients in France and to perform a literature review of lupus and HAE studies.

Case detection and data collection (a standardized form) were performed, thanks to the French Reference Center for Kinin-related angioedema.

Data were collected from 6 patients with type 1 HAE and lupus in France; no cases of systemic lupus erythematosus were reported. In the literature review, 32 cases of lupus combined with HAE were identified, including 26 female patients. The median patient age at the time of first reported HAE symptoms and at diagnosis were 17.5 years (range, 9–41 years) and 19 years (range, 9–64 years), respectively for our 6 patients and 14 years (range, 3–30 years) and 17 years (range, 7–48 years), respectively, for the literature review. The clinical manifestations of HAE were mainly abdominal pain (83% in our patients vs 47% in the literature) and edema of the limbs (83% vs 38%). The C4 levels were low (for 100% of our cases vs 93% in the literature). Eighteen patients in the literature demonstrated HAE symptoms prior to the lupus onset vs 5 for our patients. The mean patient age at lupus onset was 20 years (range, 13–76 years) for our patients and 19.5 years (range, 1–78 years) in the literature, respectively. In the literature, 81% of the patients had skin manifestations, 25% had renal involvement and 28% received systemic steroids to treat lupus. Treatment with danazol did not modify the clinical expression of lupus. The association between lupus and HAE is a rare but not unanticipated event. Patients are often symptomatic for HAE before developing lupus. Lupus cases associated with HAE share some characteristics of lupus cases related to other complement deficiencies, such as the absence of severity and the predominance of cutaneous symptoms.

Contents

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1. Introduction

Hereditary angioedema (HAE) is a rare condition that leads to recurrent swelling of subcutaneous and mucosal tissues. HAE can cause abdominal pain, swelling of the face and limbs, and in severe cases, tracheal involvement can lead to asphyxia. HAE was first described by William Osler in 1888 [1]; with autosomal dominant heterozygous transmission, homozygote forms exist but are rare [2].

HAE is related to C1 inhibitor (C1-INH) deficiency. Two types of HAE related to C1-INH have been described: type 1 HAE is characterized by the deficit of C1-INH production; in type 2 HAE, C1-INH levels are normal, but there is decreased C1-INH activity. Complement components 4 (C4) and 2 (C2) are known to be low in HAE [3], in relation to the lack of C1-INH, which leads to activation of the classic complement pathway. A third type of HAE has been described by Bork [5]; type 3 HAE, which is characterized by normal C1-INH (as opposed to types 1 and 2 HAE), with Factor 12 mutations (gene encoding for the Hageman factor) in 15 to 20% of patients [6].

Associations between HAE and auto-immune diseases have been described, with a 2% [3] to 12% [4] prevalence. Lupus, either cutaneous or systemic lupus erythematosus (SLE), is the most often described autoimmune condition associated with HAE [7–9]. The pathophysiology is supposedly linked to the modification of complement metabolism [9,10], leading to production or accumulation of immune complexes and decreased viral clearance. Components of the classical complement pathway are of interest because patients with C4 and C2 deficiencies often develop autoimmune diseases, most frequently SLE [11]. Other autoimmune or inflammatory conditions have been described in association with type 1 and 2 HAE [4], but to date, there are no data concerning the autoimmune disorders in type 3 HAE.

The aims of the present study are (i) to describe the HAE cases associated with lupus in France and (ii) to perform a literature review of the association of lupus and HAE.

2. Patients and methods

2.1. Patients

All internal medicine physicians were asked to report cases of HAE with associated lupus to the National Society of Internal Medicine (SNFMI) and the French National Reference Center for Hereditary Angioedema (CREAK). Data were retrospectively collected from medical files using a standardized form.

We included patients diagnosed from 1970 to 2013 at 7 French centers.

Clinical, biological, immunological and genetic data were collected for each case, as well as the treatments for HAE and lupus. The immunological data consisted of (if available) antinuclear factors (ANF), extractable nuclear antigens (ENA), and double stranded DNA antibodies (dsDNA).

HAE type 1 and 2 diagnoses were defined as the presence of decreased activity and concentration for type 1 HAE and normal concentration and decreased activity for type 2 HAE. The patients with clinical features consistent with HAE and normal C1-INH with the mutation in the F12 would be considered to have type 3 HAE in this study.

The SLE diagnosis was made using the conventional international criteria of the American College of Rheumatology (ACR). Cutaneous lupus diagnosed as the presence of characteristic cutaneous features (i.e., discoid lupus, acute erythematosus lupus, subacute lupus) in the absence of systemic involvement. Among our cases, if the patients had articular manifestations but did not fulfill the ACR criteria, they were diagnosed as cutaneoarticular. In the literature, references were often made to "SLE-like", meaning lupus with systemic symptoms that did not fulfill the ACR criteria. When available, the skin biopsy results were collected and were considered to be cutaneous lupus in the presence of consistent histology; the presence of a lupus band was noted in cases of immunoglobulin and/or complement deposit at the dermoepidermal junction under immunofluorescence.

2.2. Statistical analysis

Data are expressed as the medians with ranges [min–max] for continuous variables and as frequencies with percentages for qualitative variables. The Fisher test or Chi-squared test was used for qualitative variables, and the Student *t*-test or Mann–Whitney *U*-test was used for quantitative continuous variables. Analyses were performed with R software version 3.1.0.

2.3. Literature review

The literature search was performed by one investigator (IGS) using Medline, Embase and World of Science from 1970 to 2013. The following keywords were used for HAE: hereditary angioedema, C1-inhibitor deficiency, hereditary angioneurotic edema, complement deficiency state; and for lupus: systemic lupus, lupus-like syndrome, cutaneous lupus, lupus erythematosus; autoimmune diseases, immunoregulatory disorders. All case reports and original articles published in peer-reviewed journals were included in the literature review.

3. Results

Six patients with HAE and lupus were included (Table 1). Five patients were women, and the median age at the time of HAE symptom onset and diagnosis were 17.5 years (range, 9–41 years) and 19 years (range, 9–64 years), respectively. The median HAE diagnostic delay was 1 year (range, 0–39). The following worsening or triggering factors of HAE were identified in 4 patients: pregnancy (n = 2), physical stress (n = 1), psychological stress (n = 2), menopause (n = 1), and dental care (n = 1).

The median age at lupus onset was 20 years (range, 13–76 years). There were no cases of SLE and no cases of renal involvement. Two patients had articular manifestations (patients 4 and 5); all patients presented with cutaneous manifestations. Patient 3 had subacute lupus. All lupus patients received hydroxychloroquine, except for one patient who only received topical corticosteroid treatment. Five of 6 patients had ANF; 4 of these patients had anti-SSA antibodies. One patient had a skin biopsy that was compatible with lupus (patient 4), the other had a non-conclusive biopsy and no lupus band (patient 6). All patients had low C4 levels. Four patients had already been treated with danazol, with good effects (2 with tranexamic acid, 1 with icatibant, and 2 with C1-INH concentrate). None of the patients reported any effects of those treatments on the course of their lupus.

The literature review (Table 2) found 32 cases of HAE associated with lupus [4,8–10,12–29]. The median ages at HAE onset and diagnosis

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