
Chronic idiopathic urticaria: a family study

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Background: Genetic factors play a pivotal role in the pathogenesis of many autoimmune disorders. Recent studies demonstrated that chronic idiopathic urticaria (CIU) is an autoimmune disease at least in a subset of patients, but familial studies have not yet been conducted.

Objective: To investigate the familial pattern of CIU.

Methods: One thousand three hundred eight adults with CIU (aged >12 years; male/female 388/920) seen during the last 10 years were thoroughly interviewed to ascertain the presence of CIU among first-degree relatives. Positive histories were confirmed by medical recordings. Proportions were compared with those expected in the general population on the basis of a 0.1% prevalence of the disease.

Results: Fifty-six of 1,308 (4%) patients had a familial history of CIU affecting at least one first-degree relative. This number exceeded by approximately eight times the expected one ($P < 0.001$). Twenty-two of 23 (96%) patients with a positive familial history were positive on autologous serum skin test ($P < 0.01$ by comparison with previous studies).

Conclusion: The observation that CIU is much more frequent among first-degree relatives of affected individuals than in the general population suggests the existence of a genetic background for the disease and provides a clinical support to the reported association between CIU and human leukocyte antigen DR4. Ninety-six percent of patients with a positive familial history were positive on autologous serum skin test, a condition that has been associated with the presence of circulating histamine releasing factors, including anti-Fc ϵ RI or anti-immunoglobulin E antibodies.

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INTRODUCTION

It is generally believed that both hereditary and environmental factors play a pivotal role in the pathogenesis of many autoimmune disorders. As a consequence, the understanding of genetic and epidemiologic determinants may be critical to unravel the etiology of a possibly autoimmune disease. Chronic idiopathic urticaria (CIU) is a skin disorder characterized by the recurrence of transitory, itchy wheals for more than 6 weeks. Its origin has been unclear until it was found that up to 60% of patients with active disease show a wheal-and-flare reaction upon intradermal injection of autologous serum, and that sera from patients with CIU frequently show histamine-releasing properties attributable to circulating anti-immunoglobulin (Ig)E or anti-Fc ϵ RI (the high-affinity IgE receptor) IgG, or to a not-yet-characterized 30-kD serum factor.^{1–10} On the basis of these findings, an autoimmune pathogenesis, at least for a subset of patients with CIU, has been suggested. This fact seems also indirectly confirmed by the frequent association between CIU and thyroid autoimmunity.^{11,12} Recent studies showing an association with human leukocyte antigen DR4^{13,14} suggest a genetic background for this skin disease, but epidemiologic analyses have not yet been conducted. The present study investigated the familial pattern of CIU.

PATIENTS AND METHODS

Patients

All 1,308 adults (aged >12 years; male/female 388/920) diagnosed as having CIU at this allergy center during the last 10 years were studied. In all cases, known causes of urticaria such as food allergy, additive intolerance, parasitoses, or systemic diseases had been excluded by appropriate investigations. Patients with physical urticaria were not included in this study. At the first visit all patients underwent a thorough interview aiming to ascertain the presence of CIU among first-degree relatives (parents, siblings, and/or offspring). In the presence of a possibly positive familial history, patients were asked to show us the medical recordings confirming diagnosis of CIU in their relatives during one control visit. In the absence of adequate medical diagnosis, positive histories were not considered.

Up from September 1, 1997, all patients underwent the autologous serum skin test (ASST) as previously described.¹⁰

Statistics

The number of affected relatives was compared with the number expected on the basis of a 0.1% prevalence of the disease in the general population.^{4,15,16} In the absence of any hereditary factor, and considering an average of five first-degree relatives per patient, the expected prevalence of CIU among relatives of the 1,308 patients was estimated to be seven. Statistical analysis was carried out by the χ^2 test with Yates corrections. Probability (P) values <5% were considered significant.

RESULTS

Fifty-six of 1,308 (4%) patients with CIU seen at this allergy center during the last 10 years had a family history of CIU affecting at least one first-degree relative (diagnosis con-

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firmed by medical recordings). This number exceeded by approximately eight times the expected one ($P < 0.001$). As 14 couples ($n = 28$) of first-degree relatives with CIU were directly seen at this allergy center in different times, the 56 subjects with a positive familiar history belonged to 42 distinct families. Three female patients had two first-degree relatives affected by CIU: sister and son (the son was also directly seen), mother and brother, and two sisters, respectively. Altogether, the 44 family ties between patients affected by CIU were the following: father/son ($n = 2$), father/daughter ($n = 4$), mother/son ($n = 6$), mother/daughter ($n = 10$), brother/brother ($n = 2$), brother/sister ($n = 6$), sister/sister ($n = 14$).

Twenty-three of 56 patients with a familial history of CIU underwent the ASST; 22 (96%) of these were positive. This proportion is significantly higher than the one recently found¹⁰ in consecutive patients with CIU (67%; $P < 0.01$).

DISCUSSION

It is well known that genetic factors underlie many autoimmune disorders. Most of them show a marked sex predominance, and their prevalence among relatives of affected patients is significantly higher than in the general population; further an association with specific antigens of the major histocompatibility complex (often of class II) has been frequently found. All these features can be observed in chronic urticaria, a disorder whose autoimmune origin has been recently demonstrated. The observation that CIU is much more frequent among first-degree relatives of affected individuals than in the general population suggests the existence of a genetic background for CIU and provides a clinical confirmation to the reported association between CIU and human leukocyte antigen DR4.^{13,14} The relevance of genetic factors in the pathogenesis of CIU is also suggested by the marked female predominance of the disease.^{10,17,18} Interestingly, in CIU the female/male sex ratio increases in patients showing thyroid autoimmunity¹² or circulating anti-FcεRI or anti-IgE autoantibodies.¹⁹ Finally, 96% of patients with a positive familiar history were positive on ASST, suggesting the presence of circulating histamine-releasing factors. Recent studies showed that, at least in some patients, a positive ASST is associated with the presence of circulating anti-FcεRI or anti-IgE autoantibodies.^{1,3,4,20}

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