Allergol Immunopathol (Madr). 2016;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

The predictive factors for remission of chronic spontaneous urticaria in childhood: Outcome from a prospective study

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Received 8 December 2015; accepted 27 April 2016

KEYWORDS
Chronic urticaria;
Remission;
Predictive factors

Abstract
Background: There are few studies in children on the natural course of chronic spontaneous urticaria (CSU) because of its relative infrequency in childhood.
Objective: To estimate the rate of remission and evaluate the prognostic factors in children with CSU.
Method: A total of 52 children with CSU were prospectively followed over a period of three years.
Results: The remission rates at 12 months and 36 months were 32.7% and 48.1%. The mean duration of disease at the first visit in the non-remission group was higher than in the remission group at the end of the study ($P = 0.016$). The remission rate of the patients who had been treated by standard dose antihistamine was higher than that of the patients who had been treated with the high-dose antihistamine and combination medications ($P = 0.004$, $P < 0.001$). The treatment steps were independent prognostic factors for remission by logistic regression analysis.
Conclusion: Our study indicates that urticaria controlled by a standard dose of antihistamine can predict a good prognosis independently from disease duration at first visit.

Introduction

Chronic urticaria (CU) in childhood is a rare and challenging disease for both patients and doctors because it is a long-term disease and there are limited data about its natural course. It is characterised by short-lived itchy wheals occurring at least twice a week and persisting for six weeks or longer.[1-3] The causative factors, such as physical factors, food allergy, drug reaction, connective tissue disease, chronic infection, and parasitic infestation are identified in <30-40% of patients with CU.[4,5] The diagnosis of chronic idiopathic urticaria (CIU) is made when no apparent trigger

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http://dx.doi.org/10.1016/j.aller.2016.04.011
0301-0546/

Please cite this article in press as: Eser I, et al. The predictive factors for remission of chronic spontaneous urticaria in childhood: Outcome from a prospective study. Allergol Immunopathol (Madr). 2016. http://dx.doi.org/10.1016/j.aller.2016.04.011

or other cause is identified. Although accurate data on the prevalence of CSU are unavailable in children, this condition is thought to affect 0.1–3% of adults in the United States and Europe.[1] The presence of histamine-releasing IgG anti-FcRI and anti-IgE autoantibodies suggests an autoimmune pathogenesis of disease in a subset of patients; 31–47% of children with CSU have an autoimmune cause with a positive autologous serum skin test (ASST).[6–9]

CSU is an unpredictable disease. There is limited literature regarding the prognosis of CSU, and most relates to adults.[10–12] Only a few studies on the natural course of the disease have been performed on children.[6,8,13,14] Although some studies on adults have suggested that a positive ASST result, the presence of angio-oedema and positive anti-thyroid antibodies might indicate a long disease duration, we still know little about the association between the natural course and the clinical/laboratory parameters of CSU in children.[11]

The aim of this prospective study was to investigate the natural course and prognostic variables of CSU in childhood.

Methods

The study was performed in the Department of Paediatric Allergy and Immunology at Kocaeli University, Turkey, from January 2012 to January 2015. The study included children with urticaria present daily or almost daily for duration of at least 6 weeks.

At the screening visits, all patients underwent a detailed history, and physical examination. In all instances, personal history of atopic diseases (such as atopic dermatitis, asthma, allergic rhinitis), any drug intake, presence of associated angio-oedema, signs of infection (such as upper airway infection, urinary tract infection, fever), signs of connective tissue disease and auto-inflammatory syndromes (such as arthritis, arthralgia, fever, conjunctivitis, muscle and skin tenderness after exposure to cold, sensorineural hearing loss), trigger of urticaria (such as cold, exercise, hot shower), and recent travel history were investigated. In addition, family history of urticaria, atopic disease and autoimmune conditions were recorded. Skin prick tests with commercial allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, grass, tree and weed pollens, *Alternaria*, *Penicillium* and *Aspergillus*, dog and cat epithelia, milk, egg, soy, peanut, hazelnut, fish, wheat) and provocation tests for physical urticaria were performed on patients with a suggestive history.

To investigate the known causes of CU, the patients underwent the following laboratory workup: (i) complete blood cell count, blood chemistry, erythrocyte sedimentation rate, liver function tests; (ii) infective panel (serologic assays for hepatitis A and B virus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), urine analysis and culture, throat culture, *H. pylori* IgG antibodies and three stool examinations for parasites); (iii) autoimmune panel (anti-nuclear antibody (ANA), anti-thyroglobulin (anti-TG) antibody, anti-thyroperoxidase (anti-TPO) antibody, free T4, thyroid-stimulating hormone).

At the first visit, the patients without a clearly defined cause were enrolled based on exclusion criteria that included isolated physical urticaria, atopic dermatitis, infectious diseases, connective tissue diseases, auto-inflammatory syndromes and food hypersensitivity. Informed consent was obtained from the parents. ASSTs were performed on all patients. The patients were followed up every four weeks. After follow-up at least one year, the patients were allowed to leave the study if they had been in remission.

Autologous serum skin test

The patients discontinued short-acting antihistamines for at least three days. Briefly, 0.05 ml of sterile, fresh, undiluted autologous serum or 0.9% sterile saline as a negative control was injected intradermally into the volar aspect. A skin prick test with histamine (10 μg/ml) was used as a positive control. Wheal and flare reactions were recorded after 30 min. An ASST was considered positive when the wheal diameter was 1.5 mm or greater compared with that elicited by saline.

Urticaria activity score

Disease activity was assessed with an urticaria activity score (UAS). Daily assessments for key urticarial symptoms were recorded by the patients, or parents if patients were young, wheal number (range 0–3) and pruritus intensity (range 0–3), which were added together (range 0–6). The UAS7 is the sum of the scores from seven consecutive days (maximum 0–42).

Treatment

The second-generation H1-antihistamine at the standard dose for age was initiated in the patients who did not receive the H1-antihistamine treatment (step 1). The dose increased up to fourfold if urticaria was not controlled (step 2). If urticaria was not controlled, combination therapy was used including high-dose antihistamine plus montelukast and/or ranitidine (step 3). The dose increased or combined with montelukast and/or ranitidine for patients treated with the second-generation H1-antihistamines already at the referral time. Remission was considered if symptoms did not recur for at least three months without drugs.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov–Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as means ± standard deviation or median (interquartile range), and categorical variables were expressed as counts (percentages). Comparisons of continuous variables between the groups were performed using the Student *t* test and the Mann–Whitney *U* test. Comparisons of categorical variables between the groups were performed using the Pearson, Fisher, Yates, Monte Carlo χ^2 test. Logistic regression analysis was used to assess the independent association between the factors that differed significantly in the remission and non-remission groups based on univariate analysis. A two-sided *P* value <0.05 was considered statistically significant.

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