Case Report

Chronic autoreactive urticaria at six years of age

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Abstract. A case of chronic urticaria in a child 6 years old is described. The strong skin reactivity upon intradermal injection of autologous serum suggested an autoreactive pathogenesis; however, patient's serum was unable to induce histamine release from basophils in-vitro, indicating the presence of a histamine-releasing factor specific for mast cells, and possibly other than an anti-FcεRI or anti-IgE antibody. Intradermal test with autologous serum may be useful in revealing the autoreactive nature of chronic urticaria and can avoid a frustrating search for other causes of the disease. In children presenting with chronic or recurrent urticaria the diagnostic workup should include the autologous serum skin test.

Key words: autologous serum skin test, childhood, chronic urticaria.

Introduction

Chronic urticaria (CU) is characterized by the repeated occurrence of short-lived cutaneous wheals accompanied by redness and itching for more than six weeks [1]. CU has long been considered as a "mysterious" disorder and although it has been often ascribed to intolerance to foods, food dyes and food additives, in most cases hypoallergenic diets have been devoid of clinical benefit. Chronic urticaria is now recognized as an autoreactive disorder in a substantial fraction of patients [1]. In 1986 Grattan et al. showed that intradermal injection of autologous serum induced a wheal and flare reaction in many CU patients [2]. The main serologic mediator of whealing was subsequently shown to be an autoantibody directed against the α subunit of the high affinity IgE receptor (FcεRI) [3,4], which was found in about 25 percent of CU patients. This observation was confirmed by independent researchers [5,6]. In a minority of CU patients (about 5 percent) circulating autoantibodies directed against IgE can be detected. Up to 60 percent of CU patients show a wheal and flare reaction following intradermal injection of autologous serum, but anti-FcεRI or anti-IgE autoantibodies can be detected only in 30 percent of patients. Therefore, the remaining CU patients with positive autologous serum skin test (ASST) but without anti-FcεRI or anti-IgE autoantibodies have an as yet unidentified histamine-releasing factor.

Although some series of children with CU have been reported in the past [7-9], this disease is quite rare in childhood [10]. Most studies regarding the etiology and the pathogenic mechanism of CU have been conducted in adults [11]. We describe a case of CU with positive ASST occurring in a 6 year-old boy.

Case report

A 6 year-old boy with a 3-month history of recurrent, severe angioedema episodes (penis, eyelids, lips) was seen at the outpatient allergy clinic. His mother reported that the angioedema episodes had never been associated with urticaria, and that she did not observe isolated wheals of frank urticaria episodes before. The patient was otherwise well, and did not have a family history of allergic disorders or of angioedema. Physical examination was normal, as were chest X-ray

Table 1. Basophil histamine release assay results.

	Anti-IgE	Child	Control 1	Control 2
Experiment 1	45.1%	1.9%	11.7%	ND
Experiment 2	64.7%	0%	10.3%	7.4%
Experiment 2 (lactic acid stripping)	23.4%	1.4%	2.7%	9.5%

Results are expressed as percent histamine release.
ND: Not done.

examination and blood tests, including complete blood counts, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, complement fractions (C3 and C4), C1 inhibitor concentration and total IgE levels. Skin prick tests with a large series of inhalant (Allergopharma, Reinbeck, Germany) as well as food (Dome/Hollister- Stier, Spokane, Wa, USA) allergens were negative. Some days after the first visit the boy complained of itching in the neck, where his mother noticed some unequivocal wheals. After obtaining informed consent from the parents, an autologous serum skin test (ASST) was carried out according to the method described by Sabroe et al. [12]: 0.05 ml of sterile, fresh autologous serum and 0.05 ml of saline as negative control were injected intradermally. Skin tests were read after 20 min. Autologous serum induced a marked wheal-and-flare reaction (mean diameter 15 mm), whereas saline did not induce any reaction. An anti-histamine therapy was started (cetirizine 5 mg once a day). The boy is currently well and did not experience further urticaria/angioedema episodes for the last two months. The ability of patient's serum to induce in-vitro histamine release from basophils of 2 normal donors was assessed as well, using an automated fluorometric method, as previously described [13]. Results were expressed as net percent histamine release over total histamine content. A 5% net histamine release was used as cutoff. In addition, in order to detect the presence of functionally active anti-FcεRI autoantibodies, basophil histamine release was evaluated after stripping of membrane-bound IgE with lactic acid. Mixed leukocyte suspension from a normal donor was treated with 10 mmol/L lactic acid (pH 3.9) for 3.5 minutes at room temperature, a procedure that allows dissociation of FcεRI-bound IgE without damaging basophil functional activity [14]. Basophil stimulation with an optimal dose of goat polyclonal anti-human IgE (10 mg/ml; Sigma Chemical, St. Louis, MO, USA) and the serum from the CU patient was carried out as previously described, and histamine concentration in the cell supernatant was measured as described. The serum of two adult patients with CU previously shown to contain anti- FcεRI and anti-IgE antibodies, respectively, were tested in parallel with the child's serum as control.

In these in-vitro experiments the patient's serum did not induce any significant basophil histamine release either before or after stripping of membrane IgE by lactic acid. In contrast, anti-IgE-induced histamine release decreased from 65% to 23% after stripping of membrane IgE. The sera from both control patients induced significant basophil histamine release (table 1); after IgE stripping from basophils with lactic acid, one serum (containing anti-IgE autoantibodies) lost its histamine releasing activity, whereas the other (containing anti-FcεRI antibodies) showed a slight increase in histamine releasing activity.

Discussion

CU is rare in childhood. In addition to the idiopathic form, physical urticarias, urticarial vasculitis, urticaria pigmentosa (cutaneous mastocytosis), papular urticaria and Muckle-Wells syndrome have been described in children and adolescents [10]. However, the experience on pathomechanism and treatment of CU in children is much more limited than in adults. ASST is not performed routinely in children with CU, and it is not known how many patients do have an autoreactive disorder. To our knowledge, published data on the search for anti-FcεRI and anti-IgE antibodies in young CU patients are limited to 7 cases [10]. Evidence of the presence of serum anti-FcεRI antibodies has been found in 3 out of 7 CU patients with ages ranging between 10 and 16 years. The present study is probably the first one reporting a positive ASST in a child with CU as young as 6 years. The strong reactivity observed on ASST suggested an autoimmune origin of the disease, possibly associated with anti-FcεRI or anti-IgE antibodies, but in-vitro basophil histamine release assay did not confirm this hypothesis. As observed in many adult patients with CU and positive ASST, the serum of our young patient was able to induce significant histamine release from skin mast cells in-vivo but not from basophils in-vitro [13]. This finding suggests that a histamine-releasing factor specific for mast cells, and possibly other than an anti FcεRI or anti-IgE antibody may play a role in CU at all ages. The presence of a serological mediator of whealing active on mast cells and not on basophils has been recently suggested by other authors reporting on histamine-releasing autoantibodies and CU pathomechanism in adult patients [15].

Although the demonstration of the autoreactive nature of CU does not substantially change the therapeutic approach either in adult or in young patients, we suggest that ASST may be useful in elucidating the pathomechanism of the disease and can avoid a frustrating search for other causes of the disease. In children presenting with chronic or recurrent urticaria the diagnostic workup should include ASST.

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