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Chronic Autoimmune Urticaria in Children

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SUMMARY Results of determination of circulating histamine releasing autoantibodies using histamine release urticaria test in 12 children (aged 3 to 18 years, mean age 8.5 years; 7 female and 5 male) with chronic urticaria are presented. Standard work-up including detailed history, allergy testing and routine laboratory findings did not disclose any plausible cause of chronic/recurrent urticarial eruption in these children. All children underwent serum-induced basophil histamine release urticaria test. At serum dilution of 12.5%, the mean percent of histamine liberation was 40.8% (range 18%-77%; normal <16.5%), which indicated the presence of autoantibodies to FcεRIα and/or to the IgE-FcεRI complex. The percent of histamine release did not correlate with patient age or duration and severity of symptoms. Thus the autoimmune basis of chronic urticaria was established. Associated antithyroid autoantibodies were found in two patients. Complete or partial remission was obtained with treatment that included antihistamines, low salicylate-low preservative diet in all, and high dose intravenous immunoglobulin in 3 children.

KEY WORDS: child, chronic urticaria, histamine release-urticaria test

INTRODUCTION

Chronic urticaria (CU) is a clinical skin affection marked by wheals, erythema and itching that appear transiently or persist up to 24 hours, and recur for 6 weeks or more (1,2). Health-related quality of life is significantly influenced by recurrence and duration of patient symptoms (3). Dermal mast cell degranulation and mediator release (histamine and cell-cell signaling molecules) are thought to play a central role (4). The precipitating stimuli may include pressure, stroking (dermographism), water immersion (aquagenic urticaria), solar ultraviolet radiation, cold exposure, increase in central body temperature (fever, physical effort, sweating: cholinergic urticaria). Ingested chemical substances known to induce mast cell degranulation, e.g., salicylates, preservatives, opiates and non-steroidal antiphlogistics, are often implicated in the chronicity and flare-ups. Chronic bacterial and viral infections (*Helicobacter pylori, Yersinia enterocolitica*, hepatitis B, Epstein-Barr virus and possibly chronic focal infections in the ear-nose-throat region) or collagen vascular diseases can produce the clinical condition of chronic urticaria (5).

The term chronic idiopathic urticaria (CIU) has been used to describe the set of patients with no overt underlying disease. In a significant number of these patients (30%-60%, varying by source) it has been possible to prove the autoreactive nature of CIU by indirect *in vivo* identification of own humoral factors inducing local wheal to intradermally injected autologous serum (autologous serum skin test, ASST), or *in vitro* by measuring patient serum induced donor basophil histamine

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release (Histamine Release-Urticaria test; HR-urticaria test) (6-8). The latter test detects the presence of the IgG_1 and IgG_3 subclass autoantibodies directed against the α-subunit of the high-affinity IgE receptor (FcεRIα) and/or the IgE antibody itself when bound to the FcεRI on the mastocyte (9). Besides these autoantibodies, specific differences in the expression of FcεRI-signaling molecules in the basophils or mast cells of CIU patients seem to be emerging as factors in the persistence of urticarial eruptions (10).

Chronic autoimmune urticaria seems to be as common in children (30% of CIU) as in adults (30%-40%) (11). According to current recommendations, the HR-urticaria test should be used to confirm positive results of ASST in patients with CU (12). The present paper is aimed to present the results of determination of circulating histamine releasing autoantibodies using HR-urticaria test in 12 children with CU.

PATIENTS AND METHODS

In the period from September 2003 to February 2006, 13 children (aged 3 to 18 years, mean age 8.5 years; 7 female and 5 male) with CIU were found to be on the HR-urticaria test. Photographing (Figs. 1-4) was done before therapy. All study children were referred for allergy diagnosis and had been under previous dermatologic outpatient surveillance receiving chronic or intermittent antihistamine therapy. None was taking steroids or immunosuppressive therapy at the time of investigation. In six patients, no provocative factors could be identified (Table 1; Figs. 1 and 2). Antihistamine therapy was stopped at least 14 days before skin testing or serum sample collection.

Figure 1. Chronic urticaria manifesting as erythema multiforme in patient 11.

Table 1. Clinical features of 12 children with chronic urticaria

No.	Initials/ gender	Age (months)	Symptoms	Duration (weeks)	Initial trigger	Trigger	Associated disorder
1	A.D., m	56	u, purpuric	7			
2	B.M., f	42	u	11			
3	FN, f	156	u	10	Engerix? 12 days before		
4	J.D., m	156	u, ae	44	CMV acute infection + penicillin, azithromycin	antipyretics, antibiotics, expectorants; stroking, pressure	alopecia areata
5	K.M., f	61	u	47	cefuroxime, expectorant, azithromycin	aquagenic, warm environment	
6	K.K., f	132	u, ae	12			cerebral AV malformation
7	K.J., m	97	u,	71			
8	M.M., f	172	u	8	ibuprofen,Vegeta, Nutela	stroking	
9	O.K., f	110	u, ae	22			
10	P.P., f	82	u, plaques	12	melted cheese, chocolate dessert	aquagenic, stroking	
11	Š.S., m	60	em	67		stroking, pressure	
12	B.S., m	103	u	72			

f – female; m – male; u – urticaria; ae – angioedema; a – anaphylaxis; dg – dermographism; em – erythema multiforme; CMV – cytomegalovirus

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Figure 2. Dermographism in patient 8.

Standard work-up included full past medical history, physical examination, skin prick test, complete blood count, blood chemistry, C-reactive protein, antistreptolysin-0-antibodies, immunoglobulins, serum complement components C3 and C4, and total and specific IgE. All children underwent serum-induced HR-urticaria test. Prick testing included a battery of standard inhaled and food allergens as well as preservatives.

The concentration of total IgE was determined by the Microparticle Enzyme Immunoassay (MEIA) method and reagents (Abbott, USA). The analysis is based on the 'sandwich' technique and antigen-antibody complex labeling (13). The method sensitivity is 0.048 IU/L (data from package insertion).

The concentration of allergen specific IgE was measured by UniCAP method, a 'second-generation' *in vitro* method (Phadia, Sweden), where high sensitivity is achieved by use of a three-dimensional cellulose carrier (14). The confidence interval is from 0.35 kU_A/L (class 1) to 100 kU_A/L (class 5). Class 0 defaults values up to 0.35 kU_A/L, and class 6 defaults values over 100 kU_A/L. Calibrators for determination of total and specific IgE were calibrated according to the World Health Organization Second International Reference Preparation for Human IgE (WHO 2nd IRP 75/502).

Table 2. Diagnostic work-up and treatment

No.	HR-test (%)	Prick test	Total IgE (kU/L)	Specific IgE (kU_A/L)	ALT (U/L)	Thyroid antibody	IVIG	Therapy	Outcome
1	35	0	120.6	egg white, peanut <0.35	13	hTgAb <20 kIU/L	not tolerated	loratadine, CS	partly controlled
2	36	0	13		18			cetirizine	partly controlled
3	66	0	28.6		17	hTgAb <20 kI/L		loratadine	controlled
4	24	0	141.4	Penicilloyl G, Penicilloyl V, Amoxicilloyl: <0.35	9	hTgAb 25.0 kIU/L (<20)	1 treatment	loratadine	controlled
5	54	0	7	*Dermatophagoides pteronyssinus*, Penicilloyl G, Penicilloyl V, Amoxicilloyl: <0.35	14	TPO 10.43 kIU/L (<50) ANA negative		loratadine	controlled
6	77	0	110		23	hTgAb 46.7 kIU/L (<20), TSH 8.5 mIU/L (0.40-4.2)	refused	loratadine, montelukast	partly controlled
7	18	0	237		16		recommended	loratadine	partly controlled
8	20	0	9.4	*Dermatophagoides pteronyssinus*, Dactylis, nutritive: <0.35	14	hTgAb <20 kIU/L, TPO <10 kIU/L		fexofenadine	controlled
9	22	0	275.4	Dactylis, Ambrosia, Alternaria, feathers: <0.35	11	hTgAb <20 kIU/L	1 treatment	loratadine	controlled
10	61	Preservative 3+	23.2	*Dermatophagoides pteronyssinus*: 0.50	9		recommended	loratadine	partly controlled
11	47	Preservative 2+	50.2	Phadiatop: negative	28		2 treatments	loratadine	partly controlled
12	30	0	45	Penicilloyl G, Penicilloyl V, Amoxicilloyl: <0.35	28			loratadine	controlled

ALT – alanine aminotrasferase; IVIG – intravenous immunoglobulin; hTgAb – human anti-thyreoglobulin antibody; CS – corticosteroids; TPO – thyroid peroxidase antibody; TSH – thyroid-stimulating hormone; ANA – antinuclear antibodies; specific IgE for standard inhaled and food allergens was <0.35 kU_A/L (lower limit of confidence) in children No. 1, 2, 6 and 7.

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Serum-induced HR-urticaria test was performed according to the method of Stahl Skov in the RefLab, Copenhagen, Denmark (www.reflab.dk) (15). In brief, 40 μL of patient serum (presumed to contain antibodies to either FcεRIα or IgE- FcεRI complex) diluted 1:2, 1:4 and 1:8 (50%, 25% and 12.5%) respectively, was incubated with healthy donor basophil leukocytes for 60 minutes at 37 °C. Released histamine was measured using the glass fiber method. The histamine released was expressed as a percentage of histamine content. A histamine release >16.5% is considered as a positive test result, meaning that patient serum contains circulating autoantibodies, predominantly IgG_1 and IgG_3, specific for the FcεRIα or IgE-FcεRI complex.

RESULTS

All children had negative skin prick test to a panel of common inhalant and nutritional allergens (Table 2). In two patients there was a moderate positivity to preservatives (skin prick test of 2+, i.e. average wheal diameter greater than buffer and less than histamine reaction).

Total serum IgE was increased in five children, while in the remaining eight children it was below the upper reference limit in our population of children (16). Specific IgE was <0.35 kU_A/L (the lower limit of confidence) in nine (75%) children, while one child had >0.35 kU_A/L (*Dermatophagoides pteronyssinus* 0.50 kU_A/L). Seven children had thyorid antibodies tested and three were found to be positive; of these, only one girl had associated hormonal disorder and was receiving hormone replacement (Fig. 3). The remaining biochemical and hematologic findings were within the reference range. At serum dilution of 12.5%, the mean percent of histamine liberation was 40.8% (range 18%-77%; normal <16.5%) (Table 2), which indicated the presence of autoantibodies to FcεRIα and/or to the IgE-FcεRI complex. The percent of histamine release did not correlate with patient age or duration and severity of symptoms.

Figure 3. Severe urticaria in patient 6. The lesions would appear and wane in 1-2 hours. There was an associated autoimmune hypothyroidism and cerebral AV malformation. The parents refused IVIG therapy for fear of the possible encephalopathic adverse events.

Children were treated with long-term antihistamine therapy and low salicylate-low preservative diet according to a written list of potentially offending natural and commercially available nutrients (17). A satisfactory clinical response was evident within 3-6 weeks in all but three children. These were subsequently treated with high dose intravenous immunoglobulin (1 g/kg in a single infusion over 6-12 hours). Long-lasting remission was obtained in two patients, while one girl relapsed 4 weeks after IVIG, which was then repeated, with the same outcome (Fig. 4). Further treatment was limited to the diet and antihistamines.

DISCUSSION

An autoimmune pathogenesis in 12 pediatric patients with CIU was confirmed by the HR-urticaria test. Significant histamine liberation from basophil granulocytes of healthy donors was induced by the sera of patients, testifying indirectly the presence and activity of autoantibodies directed at FcεRIα and/or FcεRI-IgE complex.

Most published data refer to chronic autoimmune urticaria in adults. Recently, a few articles

Figure 4. Very discrete circinate urticarial lesions in patient 10. The parents and the child were deeply disturbed by bouts of recurrences every 3-4 days. IVIG therapy induced short lived remission.

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have dealt with chronic autoimmune urticaria in children (11,17-19). However, there is still a lack of published data on the prevalence of different types of urticaria in children, and on diagnostic efficiency of various diagnostic procedures. CU is rare in childhood. About 2.1% to 6.7% of children have urticaria (all forms, i.e. acute, intermittent and chronic) (20), and a small proportion of these children have chronic or recurrent urticaria. In the UK National Referral Centre for Urticaria, 5% of urticaria patients are children up to 16 years with CU (1). In approximately 20% of patients, infectious or physical stimuli, aeroallergens, drugs, food additives, coloring agents and preservatives could be considered as the causative and/or triggering factors (21). Triggering factors in some of our patients were preservatives, dyes, insect sting, vaccine and drugs, but in the majority the trigger could not be identified. None of our patients had a positive family history of autoimmune diseases. Only one patient in our series had another autoimmune disease. A study by Brunetti *et al*. also suggests that the relative paucity of associated autoimmune disease is attributive to the pediatric age, as the likelihood of having autoimmune diseases increases with age (11).

Standard laboratory analyses (complete blood count, urine analysis, chemistry analyses, complement components) and skin tests are usually non-informative for the evaluation of CU. Increased total and specific IgE may be found more often in CU patients and also in those with an autoimmune disorder.

CU is characterized by increased numbers of mastocytes in the dermis, which is the basis for occasional indication for biopsy or serum tryptase determination. Increased tryptase concentration is due to mastocyte activation. There is a reason to believe that patients with CU and increased serum tryptase suffer from a more severe clinical disease (22). The concentration of alpha-protryptase in serum is used in the differential diagnosis of mastocytosis (22).

The positive finding of autoantibodies directed against FcεRIα and/or the FcεRI-IgE complex is indicative of a more severe clinical disease (23,24). According to Dayenas *et al*. (25), degranulation of basophil leukocytes can be induced by very low concentration of anti-IgE antibody in the assay ($2.2x10^{-16/18}$ M). *In vitro* HR-urticaria test may depend on complement (26). As an additional argument for autoimmunity, other autoantibodies may be present. The association of thyroid autoimmunity with chronic urticaria has been reported in both adults (prevalence 14% to 33%) and children (prevalence 4.3%) (18). ANA and ANCA (antineutrophil antibodies) are only rarely positive (27). According to the results of Brunetti *et al*., the concordance between ASST and HR-urticaria test (either positive or negative) was 83% (11). Sulfidoleukotriene release and the expression of CD63 activation marker on basophil leukocytes may add to the diagnostic certainty and also to the follow up under therapy (28).

Anti-FcεRIα autoantibodies occur not only in patients with CU (38%) but can also be found in serum of patients suffering from other skin or systemic autoimmune diseases such as pemphigus vulgaris (PV; 39%), dermatomyositis (DM; 36%), bullous pemphigoid (BP; 13%) and systemic lupus erythematosus (SLE; 20%) (29). While ASST and HR-urticaria test detect biologically relevant mast cell or basophil granulocyte-activating factors, ELISA, Western blotting and immunoprecipitation can be used for identification of specific autoantibodies (29). However, although autoantibody titers in patients with PV, DM, BP and SLE were similar to those in CU patients, only CU serum samples displayed histamine-releasing activity. In addition, autoantibodies in CU patients belong mainly to complement-fixing IgG1 and IgG3 subclasses. In PV, DM and BP, they belong predominantly to IgG2 and IgG4 subclasses. Anti-FcεRIα autoantibodies were not found in healthy individuals or in patients with atopic dermatitis or psoriatic patients (29). Since C5a receptor blockade on basophil granulocytes as well as decomplementation reduced the histamine-releasing capacity of most anti-FcεRIα-reactive CU serum specimens, complement system is considered to be an augmentative and critical pathogenic factor in autoimmune-mediated CU (29).

The proof of the autoimmune mechanism in CIU offers a theoretical possibility of immunomodulatory or immunosuppressive treatment (30). The results of high-dose intravenous immunoglobulin or plasmapheresis have so far been anecdotal. Two of our patients entered long-lasting remission after IVIG therapy. Beforehand, the established treatment options should be exhausted, i.e. consistent antihistamine therapy and low salicylate-low preservative diet. If these measures fail over a period of 3-6 weeks, immunomodulatory and immunosuppressive treatment options may be considered, including high dose IVIG, corticosteroids, cyclosporine A and plasmapheresis (12).

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Joyful play in the sun and the water please body and soul. Elida cream; year 1934.
(from the collection of Mr. Zlatko Puntijar)