

Chronic urticaria and associated coeliac disease in children: A case–control study

Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, Sferlazzas C, Pajno GB. Chronic urticaria and associated coeliac disease in children: A case–control study. *Pediatr Allergy Immunol* 2005; 16: 428–432. © 2005 Blackwell Munksgaard

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Celiac disease (CD) and chronic urticaria (CU) are both sustained by immune mechanisms, but there are so far few data on their clinical association. We performed a case–control study to determine the occurrence of CD in urticaria and matched control children, and to assess the clinical relevance of this association. Children and adolescents were diagnosed to have severe chronic idiopathic urticaria in the presence of hives for more than 6 wk poorly or not responsive to oral antihistamines. Other known causes of urticaria had to be excluded. A matched control group without urticaria was enrolled. In both groups, the presence of CD was searched by assaying antitransglutaminase and antiedomysial antibodies, and confirmed with endoscopic intestinal biopsy. Results. CD was diagnosed and confirmed in 4/79 (5.0%) of children with CU and in 17/2545 (0.67%) of the controls ($p = 0.0003$). In the four children with urticaria and CD the gluten free diet (GFD) lead to complete remission of urticaria within 5–10 wk, whereas the disappearance of serological markers occurred in longer times (5–9 months). Conclusions. The presence of CD in children with CU was significantly more frequent than in controls. GFD resulted in urticaria remission. CD may be regarded in such subjects as a cause of CU.

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Key words: chronic urticaria; coeliac disease; case–control; gluten free diet

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Accepted 11 May 2005

In the field of gastroenterology and internal medicine it is nowadays well known that the overt presentation of coeliac disease (CD) as described in 1888 by Gee (1) is quite uncommon, at least in westernized countries. On the other hand it is also true that many general practitioners' still retain an image of CD that is far from the reality and based on the classical descriptions (2). The most recent clinical advances, supported by immunological data and serological assays, have clearly shown that overt cases are only a small proportion of patients with the disorder (3). In fact, silent and latent forms have been described, and the atypical forms represent the majority of the cases (4). CD is considered to arise from inappropriate TH₁ cell mediated immune response against ingested gluten in genetically predisposed people, this resulting in abnormal IgA production.

Chronic urticaria (CU) is defined as the persistence of itchy wheals (with/without

angioedema) for at least 6 wk. In the majority of cases CU is referred to as 'idiopathic,' since no specific cause can be identified, and it represents a frustrating illness for patients as well as physician, especially in children (5). In the case of CU, the underlying mechanism, when it can be identified, vary from an allergic response to an autoimmune reaction (6–8).

Given the involvement of autoimmune processes in both CD and CU, a clinically relevant association of them may be expected. Nevertheless, looking at the literature, there are only some case reports describing an association between CU and CD in adults (9–11). Similarly, in children, there are only two case reports (12, 13), and a small series suggesting a possible clinical link between CU and CD in children (14).

We wanted to test the hypothesis that a significant association between CD and CU exists in children. Therefore we performed a case–control study in a large population of

children and adolescents referred to gastroenterology and allergy units.

Patients and methods

General description

This is a case-control cross-sectional study, involving outpatients seen at the Pediatric Department of the University of Messina in the years 2000–2003. Patients with an ascertained diagnosis of severe CU, and controls (no clinical history of urticaria at all), underwent a standard procedure for the diagnosis of CD. All the subjects were from the same geographical area of Italy (Sicily). The patients' parents signed an informed consent prior to the performance of diagnostic procedures, and the study was approved by the Ethical Committee of the hospital.

Patients with severe CU

Consecutive children and adolescents with a diagnosis of CU seen at the Allergy Clinic at the Department of Pediatrics, between the years 2000 and 2003, were recruited. The clinical criteria of inclusion were: (a) clinical history of itchy hives, at least three times a week for more than 6 wk; (b) poor or insufficient control by conventional antihistamine therapy; (c) need for repeated courses (at least three times in the last 8 wk) of systemic steroids, for controlling the disease. Patients with episodes of acute urticaria only, and those well controlled with H1 antihistamines (with or without H2 antihistamines associated) were excluded as well.

All the patients fulfilling the aforementioned criteria underwent a diagnostic workup in order to exclude the most common causes of urticaria. Several laboratory parameters were assayed, including: blood cell counts, clinical chemistry and urinalysis, erythrocyte sedimentation rate, antinuclear autoantibodies, rheumatoid factor, complement fractions, circulating immune complexes, thyroid hormones and thyrothopin, anti-thyroid antibodies. Repeated stool assays for parasites and eggs were also performed. Measurement of total serum immunoglobulins, including IgA was performed in all patients. A detailed allergologic study, including total serum IgE, Skin Prick Test and RAST assays for aeroallergens and common food allergens was carried out as well. Additional studies included: paranasal sinus CT, C1qINH measurement, autologous serum skin test (ASST). The CU patients (or parents) were then required to record on a diary, every 2 wk from January to Decem-

ber, their daily symptoms and the use of chronic therapy and rescue medications.

Control patients

Schoolchildren and adolescents (up to 18 yr) were recruited at the Pediatric Clinic, with the kind cooperation of the Pediatrician General Practitioners. They had to have a completely negative clinical history for itchy hives and wheals in the past 3 yr at least. The possible presence of an already established diagnosis of CD was assessed as well. All the subjects underwent the screening procedures (detailed below), unless they had a previously established diagnosis of CD.

Diagnosis of CD

Both CU patients and controls underwent anti-Guinea pig tissue transglutaminase antibody (TGA) determination that has a very high negative predictive value and represents a good screening test. Values higher than seven arbitrary units were considered positive (15). Subjects with a positive TGA underwent determination of antiendomysial antibody (EMA) as confirmatory test. Those patients, who proved positive to both tests, underwent an endoscopic intestinal biopsy. At least three biopsy samples were taken and evaluated at histology by a modified Marsh's classification for diagnosis of CD, according to the revised ESPGHAN criteria (16).

Statistical analysis

All data were analyzed by means of a computerized program (SAS Package). The descriptive statistics was provided as mean + SD. Odd ratios (OR) and their confidence interval for CD incidence were calculated by chi-square test.

Results

Ninety-five consecutive outpatients fulfilled the diagnosis of CU. Sixteen out of them with associated diseases or secondary CU were excluded: nine had antithyroid autoantibodies (four with overt Hashimoto's disease), two had juvenile rheumatoid arthritis and five had food allergy confirmed through double blind challenge and elimination diet. Thus, seventy-nine patients (age range 2–18 yr), with idiopathic CU were the case group. Demographic and clinical data of the 79 patients with CU are shown in Table 1. Some of them (15/79) had positive ASST and 28/79

Table 1. Demographic data of patients with CU

No. of patients	79
Sex (M/F)	38/41
Age (mean in yr)	7
Age (range in yr)	2–18
Associated allergic diseases	
Asthma	10
Atopic dermatitis	5
Rhinitis	4
Asthma and rhinitis	3
Atopic dermatitis and asthma	6
Accompanying angioedema	11
SPT (+/–)	28/51
RAST (+/–)	24/55
ASST (+/–)	15/64

M/F, male/female.

were suffering from concomitant allergic diseases. Out of 79 CU patients, four children (5.0%; 95% CI 1–12%) and 17 out of 2545 (0.67%; 95% CI 0–1%) controls resulted as having CD (OR 7.7; 95% CI 2.3–23.2; $p = 0.0003$). Of note, in the control group, in eight children the diagnosis of CD had been previously established, whereas in nine the diagnosis was made during this screening. The diagnosis of CD was supported in all cases by TGA and EMA positivity and confirmed by the finding of a 3a–c degree of villous atrophy. Serum IgA were within the normal range for age in all children. Several patients in the CU had positive skin tests and/or RAST to inhalatory or food allergens, but in none case these positivities were clinically related to urticaria. In particular, in five patients with positive food skin tests (two milk, one egg, one peanut, one tomato, one codfish) both the oral challenge and the elimination diet provided negative results.

Clinical and serological features of the four patients with CU and CD are shown in Table 2. None of these four patients had positive ASST or antithyroid antibodies and only one had positive SPT and RAST assay to codfish, without clinical significance. All four children were placed on Gluten Free Diet (GFD) with complete resolution of their hives; they were able to discontinue H1 antihistamines, H2 antihistamines and corticosteroids. The symptomatic improvement preceded the normalization of antiendomysial and antitransglutaminase antibodies, which disappeared in all patients within 9 months (Table 3).

The symptoms of patient 1 improved within 7 wk of GFD. During the diet without gluten he needed twice rescue medication with cetirizine, 0.25 mg/kg/day for 3 days and 5 days, respectively. The normalization of EMA and TGA occurred within 5 months from the starting of GFD, and decline of EMA preceded that of TGA.

Patient 2 had an improvement of his urticaria within 8 wk. Regular daily treatment with cetirizine was given only during the first month of GFD, then it could be discontinued. Subsequently, a 5-day course of the same rescue medication was needed only on a single occasion during the second month. EMA and TGA disappeared within 7 months.

Patient 3 had positive IgE to cod fish (skin test and RAST), but complete avoidance of the fish was not effective on his CU. Thus, the presence of specific IgE to food was unlikely to be related to urticaria. On the contrary, GFD lead to the almost complete disappearance of hives within 5 wk, with short courses of cetirizine drops needed only on three occasions. EMA and TGA antibodies returned to normal value within 6 months after the starting of GFD.

Table 2. Clinical and lab features of the four coeliac patients

Patients	1	2	3	4
Sex	M	F	M	F
Age (yr)	6 yr	10 yr	8 yr	9 yr
Urticaria duration (months)	7	6	24	9
Allergies and associated diseases	No	No	Skin and RAST + to cod of no clinical relevance	No
Previous medical treatment	Cetirizine Steroids	Cetirizine Cimetidine Steroids	Loratadine Cimetidine Steroids	Cetirizine Oxatomide Cimetidine Steroids
ASTT	Negative	Negative	Negative	Negative
SPT	Negative	Negative	Cod fish	Negative
RAST	Negative	Negative	Cod fish	Negative
Antithyroid antibodies	Negative	Negative	Negative	Negative

M, male; F, female.

Table 3. Clinical and serological outcomes of the CD patients with CU

	1	2	3	4
EMA	Positive	Positive	Positive	Positive
Antitransglutaminase antibodies UA	12.4	8.2	16.9	18
Duration of urticaria on GFD	7 wk	8 wk	5 wk	10 wk
Time to serological normalization	5 months	7 months	6 months	9 months

EMA, Antiendomysial antibodies; GFD, gluten free diet.

Patient 4 continued to have urticaria for about 10 wk starting his GFD, and she was not able to discontinue cetirizine for at least 6 wk. Then a significant improvement was achieved and antihistamine could be discontinued. In this patient, the decrease in serum levels of TGA and EMA occurred slowly, taking 9 months to disappear. Of note, of the remaining 75 patients with CU 29 achieved remission after not less than 6 months of therapy, 23 patients still have episodes of acute urticaria, and 23 are still under chronic therapy.

Discussion

Both CD and urticaria are immuno-mediated disorders, but they differ in their pathogenesis, since CD is always a TH₁-mediated autoimmune response to gluten, whereas urticaria, due to uncontrolled degranulation of mast cells, can be sustained by a variety of mechanisms that range from a TH₂-driven response to allergens to a TH₁ autoimmunity (6). In particular, it is well known that positivity of antithyroid antibodies is more frequent in CU patients (17), and it has recently been shown that a large proportion of patients with CU have anti-IgE receptor antibodies (18). Also in children with CU, the prevalence of autoimmune urticaria is quite high (8). In this regard, a partial overlapping between CD and CU (in its autoimmune form) can be expected. Indeed, there are few case reports and a small case series concerning the association CU-CD (9, 11, 14). Of note, in all these cases, urticaria improved after starting a GFD. On the other hand, a recent study by Ciacchi et al., showed that the prevalence of allergic disorders in patients with CD was not different from that observed in a control population (19).

We undertook this case control study, in order to assess the occurrence of CD in children with idiopathic CU in comparison to a control population. Also, we attempted to assess whether CD could be involved in the pathogenesis of CU

itself. In our study population of 79 children with CU we found four patients with CD, confirmed by high serum level of EMA and TGA antibodies, and pathologic small bowel endoscopic biopsies. Thus, the rate of CD in CU patients resulted to be significantly higher than in the control population of 2545 subjects.

The ideal treatment for urticaria is identification and removal of its cause. This is usually easy to do in the case of acute urticaria, whereas in chronic forms the etiology is difficult to identify, and the treatment can only aimed to provide symptomatic relief (20). In our patients, despite the absence of overt enteropathy or malabsorption, a GFD was given. After starting the GFD, antiendomysial and antitransglutaminase antibodies invariably returned within the normal range, and urticaria remitted in parallel, as described also in recent reports (21, 22). The GFD achieved a remission in a shorter time, compared to the non-coeliac patients, where a spontaneous or drug induced remission took more than 6 months. We cannot formally exclude the possible role of an IgE-mediated allergy to wheat components, but the negative RAST and skin test to wheat in all patients, and the negative prick by prick in CD patients make this hypothesis unlikely. Indeed, an oral challenge with wheat would have ruled out this possibility, but the challenge was not performed for ethical reasons: namely the possibly worsening of bowel inflammation.

In conclusion, we hypothesize that CD maybe involved in the pathogenesis of some cases of chronic idiopathic refractory urticaria. Thus, the diagnosis of CD should be considered in children with refractory CU, even when no overt symptoms of CD are present.

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