Celiac Disease Associated With Familial Chronic Urticaria and Thyroid Autoimmunity in a Child

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ABSTRACT. An 11-year-old girl presented with chronic urticaria (CU), antithyroid antibodies, and anemia. Celiac disease was diagnosed. The family history was positive for maternally derived CU and thyroid autoimmunity in three generations. Human leukocyte antigen typing disclosed human leukocyte antigen DQA1*0501 DQB1*0201 in both mother and child. CU was unresponsive to a gluten-free diet despite clinical and laboratory resolution of celiac disease in contrast to previous reports in adults. We believe that this is the first report of this association in a child, highlighting that CU may be a part of the spectrum of autoimmune phenomenon related to celiac disease. ***Pediatrics*** **1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e25;** ***celiac disease, chronic urticaria, thyroid, human leukocyte antigen, autoimmunity.***

ABBREVIATIONS. HLA, human leukocyte antigen; CU, chronic urticaria; IgE, immunoglobulin E; IgA, immunoglobulin A; GFD, gluten-free diet; IDDM, insulin-dependent diabetes mellitus.

Celiac disease is a gluten-sensitive enteropathy known to be associated with varying extraintestinal manifestations, including autoimmune diseases.[1,2] Genetic susceptibility to celiac disease is associated strongly with the expression of human leukocyte antigen (HLA)-DQ2 allele.[3]

Chronic urticaria (CU), defined as recurring attacks of hives with or without angioedema lasting ≥6 weeks, is a disorder for which the cause is rarely determined.[4] This is in contrast to patients with acute urticaria, in which a well defined cause such as allergy to drugs, food, insect sting, or infection can be identified in ~70% of cases.[5] Currently, the concept has evolved that the disease might be autoimmune in origin at least for a subpopulation of patients. The frequency of an atopic history is no greater than that of the general population, and the serum immunoglobulin E (IgE) level is usually normal.[4] Leznoff and Sussman[6] reported a prominent association of CU with thyroid autoimmunity in adults and children, and Gruber et al[7] reported an increased incidence of anti-IgE autoantibodies in the sera of patients with CU.

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Received for publication Dec 28, 1998; accepted Mar 9, 1999.

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We describe a child with celiac disease associated with familial CU and thyroid autoimmunity to highlight another manifestation of the autoimmune kaleidoscope associated with celiac disease.

CASE REPORT

An 11-year-old white female presented with CU and fatigue. She had been well until 4 months earlier, when she developed daily migratory itchy hives and fatigue. There were occasional episodes of swelling in the lower lip or eyelids as well. Episodes were not related to specific environmental allergens, medications, or food and were not aggravated by physical stimuli such as pressure, warm water, cold, or exercise. There was no response to elimination of suspected foods. The child was a good eater and had a balanced diet; there was no history of diarrhea, bleeding, vomiting, constipation, oral ulcers, arthralgia, or use of medications. Her family history was positive for thyroid disorders in three consecutive generations and CU with a goiter in both the mother and maternal great-grandmother. Both were euthyroid. The maternal grandmother suffers from Hashimoto's thyroiditis and hypothyroidism and has never had urticaria. Maternal urticaria was well controlled with ketotifen. Previous allergy testing of the mother had been uninformative as to the cause of urticaria. The mother had an antimicrosomal antibody titer of 1/25 600, positive antinuclear antibody (1/160 speckled pattern), normal C3, C4, blood count, and urine analysis findings; and was otherwise healthy. There was no family history of celiac disease or other autoimmune disorders. An 8-year-old sibling was healthy.

Physical examination was normal aside from obvious pallor. The patient was in Tanner stage 1, and height and weight were just below the 10th percentile (expected midparental height >75th percentile). The neck was supple, and a goiter was not palpated. Laboratory evaluation revealed hemoglobin 9.1 g/dL; mean corpuscular volume 59; iron 14 mcg/dL (37–18); ferritin 0.7 pg/mL (8–72); immunoglobulin A (IgA) 241 mg/dL; IgG 1020 mg/dL; and IgE 63 IU/mL (all within normal range). Test results for C3, C4, transaminases, urine analysis, creatinine, and stool hemoccult were normal. Antinuclear factor was speckled pattern 1/80, anti-DNA, anti-Ro, and anti-La were negative. Antiendomysial and antigliadin antibodies (IgA 35 and IgG 19, normal <12 by enzyme-linked immunoadsorbent assay) were positive. Antiperoxidase antibody was 258.6 (normal <50), free T4 14.58 pmol/L, and thyroid-stimulating hormone 3.84 mIU/L (N = <4.2). Additional absorption studies were not performed.

Small bowel biopsy revealed subtotal villous atrophy with a dense plasma cell infiltrate, cuboidal epithelium, and deep crypts that are typical findings in celiac disease.

Family tree and HLA typing are provided in Fig 1. Family screening results using antiendomysial and antigliadin antibodies as well as IgA levels were normal in all other family members.

The patient was placed on a gluten-free diet (GFD) with iron supplements and responded with normalization of hemoglobin and marked weight gain within 2 months. At 3 months' follow-up, breast buds were noted; antiendomysial antibody had disappeared.

After 12 months on a strict GFD and normalization of antiendomysial antibodies, she remains in clinical remission. Urticaria has not improved but remains responsive to loratadine. Follow-up biopsy was not performed.

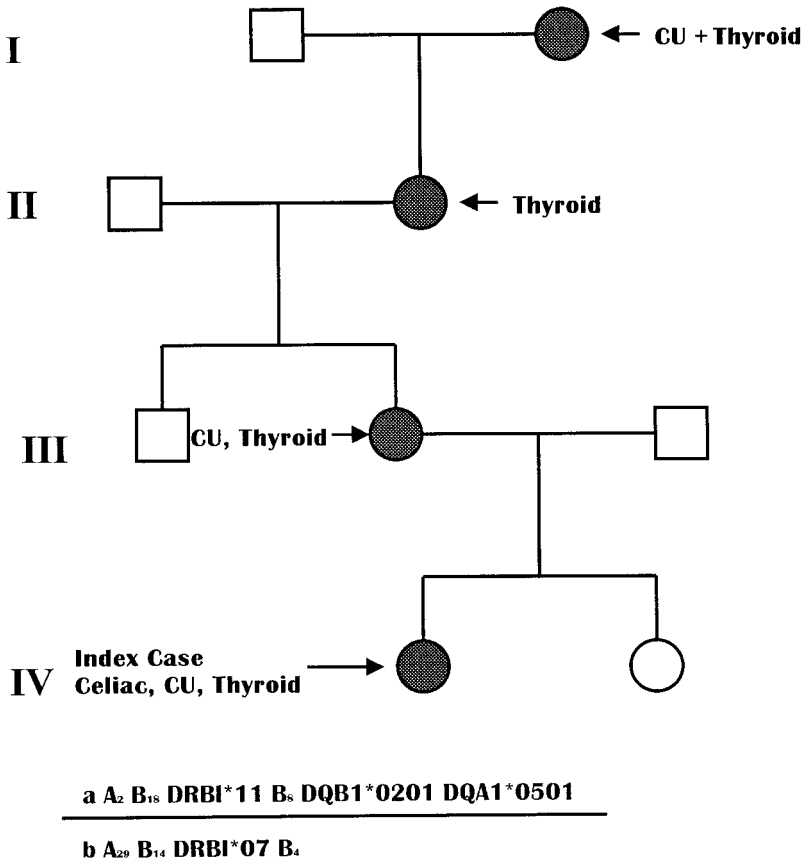

Fig 1. Family tree with HLA typing. A indicates a maternally derived allele, and B indicates a paternally derived allele.

DISCUSSION

We report here the first case, to our knowledge, of celiac disease associated with CU in a child. Factors supporting an autoimmune process in this case include the strong family history of CU associated with antithyroid antibodies in 3 family members, the presence of antinuclear antibody, and antithyroid antibodies in the patient.

Celiac disease occurs with increased prevalence in several immune-associated diseases, most notably in insulin-dependent diabetes mellitus (IDDM), dermatitis herpetiformis, and thyroid disorders. Screening of celiac patients has found a prevalence of 12% for all autoimmune disorders in one study and a prevalence of 14% specifically for thyroid disease in another study.[1,2] Conversely, when patients with autoimmune disorders are screened for celiac disease, the prevalence is also high, ranging from 4.8% for thyroid disorders to 4.8% to 6.4% for IDDM.[8–10]

Most cases of CU are considered idiopathic, because no specific allergen can be identified in >80% of patients.[4] There are several points suggesting that autoimmunity may play a significant role in the pathogenesis of CU in some of these patients.

Histopathologic biopsies of the lesions of CU reveal a perivascular accumulation of eosinophils, mast cells, and activated $CD4^+$ T cells, in contrast to biopsies of lesions in acute urticaria that are devoid of cellular infiltrates.[11,12] An increased incidence of IgG autoantibodies against the high affinity IgE receptor has been demonstrated in the serum of patients with CU.[13] Leznoff and Sussman[6] reported that 90 of 624 (14%) patients with CU had evidence of thyroid autoimmunity compared with 3% to 6% of the general population.

CU associated with celiac disease was first reported in an adult and was noted to have disappeared within 3 months of a GFD.[14] Gallo et al[15] investigated 43 adult patients with CU or atopic dermatitis for celiac disease and found biopsy-proven asymptomatic celiac disease in 3 (7%) of these patients. They followed 1 patient for 6 months on a GFD and reported improvement of urticaria on GFD. Liutu et al[16] found antigliadin antibodies in 4/107 adult patients with CU and biopsy-proven celiac disease in 2 of 107 patients. Follow-up of CU on a GFD was not reported.

Hautekeete et al[14] hypothesized that the passage of yet unknown antigens through the damaged mucosa in celiac disease may have been responsible for the pathogenesis of CU and that the restoration of mucosal integrity led to the disappearance of urticaria. Our patient did not show any improvement of her CU after institution of GFD for 1 year despite strict adherence to GFD, disappearance of antiendomysial antibodies, and clinical resolution. This observation mitigates against gluten- or external antigen-induced CU as a significant pathogenic etiology. The strong family history of CU with autoimmune thyroid disease and the absence of clinical and serologic signs of celiac disease in other family members make it more plausible that CU is another feature of autoimmunity in a genetically susceptible family. The improvement in CU after institution of GFD, noted by Hautekeete

and Gallo, might have been related to the natural history of CU.

The family history of four consecutive generations is compatible with a pattern of dominant inheritance of autoimmune-associated diseases in females. HLA typing demonstrated that HLA DQA1*501\QB1*201 (DQ2) in the child is the maternally derived allele. This allele is found in 86% to 94% of patients with celiac disease in certain populations[3,17] and can predispose children to other autoimmune diseases such as thyroid autoimmunity and IDDM.[18,19] There is evidence that this molecule plays a role in the pathogenesis of celiac disease as a restriction element for gliadin-specific T cells in the gut.[20] Recently, Molberg et al[21] reported transglutaminase modification of gliadin unmasking epitopes that can bind to HLA DQ2. Theoretically, HLADQ2 may play a role in other autoimmune diseases such as CU. It is conceivable that a common denominator in the form of HLA type in both mother and child might be the predisposing link for CU as well as for celiac disease instead of simple mendelian inheritance.

Physicians treating either celiac disease or CU should be aware of this association. Although the actual prevalence of celiac disease in patients with CU remains to be clarified, screening of appropriate patients with CU for celiac disease should be considered.

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Pediatrics 1999;104;e25
DOI: 10.1542/peds.104.2.e25

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