

Idiopathic Chronic Urticaria and Celiac Disease

MAURIZIO GABRIELLI, MD, MARCELLO CANDELLI, MD, FILIPPO CREMONINI, MD,
VERONICA OJETTI, MD, LUCA SANTARELLI, MD, ENRICO C. NISTA, MD, ELEONORA NUCERA, MD,
DOMENICO SCHIAVINO, MD, GIAMPIERO PATRIARCA, MD, GIOVANNI GASBARRINI, MD,
PAOLO POLA, MD, and ANTONIO GASBARRINI, MD

Idiopathic chronic urticaria (ICU) is a chronic relapsing cutaneous disease. Some case reports or studies on small series of celiac disease (CD) patients have suggested a possible association between CD and ICU. The aim of this study was to assess the prevalence of CD in a population of adults ICU patients with respect to healthy controls. We consecutively enrolled 80 patients affected by ICU and 264 blood donors as the control population without a history of ICU. Serum anti-transglutaminase IgG and anti-endomysium IgA antibodies were evaluated in all subjects. In the case of positivity to serology, diagnosis was confirmed by duodenal biopsy. One of 80 (1.25%) ICU patients were positive to both anti-transglutaminase and anti-endomysium antibodies. Duodenal biopsy showed partial villous atrophy. One control of 264 (0.38%) had CD. No statistical difference was found in the prevalence of CD between the two groups. ICU patients do not seem to bear a greater risk for CD compared to the general population.

KEY WORDS: idiopathic chronic urticaria; celiac disease; anti-transglutaminase antibodies; anti-endomysium antibodies; autoimmune diseases.

Idiopathic chronic urticaria (ICU) is a cutaneous disease of uncertain origin, characterized by recurring attacks of hives, sometimes associated with angioedema, persistent or recurring over 6 weeks and without the evidence of a causal agent (1, 2). Several theories have been proposed to explain the pathogenesis of ICU. The autoimmune hypothesis remains the most plausible at present (1, 2).

Celiac disease (CD) is a chronic inflammatory intestinal disease resulting from an inappropriate T cell-mediated immune response against ingested gluten in genetically predisposed individuals (3). The clinical spectrum of CD is extremely variable, ranging from the classic malabsorption syndrome to the silent forms (3). The availability of highly accurate serological markers (anti-

transglutaminase and anti-endomysium antibodies) have strongly increased the detection rate of CD in the last years (4). CD has been associated with several extraintestinal conditions, the most common being autoimmune disorders, including type 1 diabetes mellitus and autoimmune thyroiditis (5).

Some case reports and one study (6–11) on a small series of pediatric CD patients (12) suggested a possible association between CD and ICU. It has been suggested that autoimmunity evoked by gliadin or by other unknown antigens may be the linkage between ICU and CD (11, 12).

The aim of the present study was to assess the prevalence of CD in a population of adult patients affected by ICU and in healthy controls.

METHODS

Participants. Eighty patients affected by ICU were consecutively enrolled at the allergy outpatient service of our university hospital. Two-hundred sixty-four blood donors without a history of ICU were included in the study as the control population. Informed consent was obtained from each participant.

Manuscript received January 4, 2005; accepted January 11, 2005.

From the Department of Internal Medicine, Catholic University the Sacred Heart, Rome, Italy.

Address for reprint requests: Antonio Gasbarrini, MD, Department of Internal Medicine and Angiology, Catholic University of Sacred Heart, Gemelli Hospital, Largo Gemelli 8, 00168 Rome, Italy; angiologya@rm.unicatt.it.

Eligibility Criteria. Consecutive patients presenting to the allergy outpatient service were considered eligible for enrollment if they had a history of chronic urticaria for at least the previous 6 weeks and no evidence of conditions known to be associated with chronic urticaria.

Secondary forms of chronic urticaria were excluded by the following.

1. Negativity to prick, patch, and RAST tests for the most common dietary (cereals, fish, shrimps, nuts, milk, eggs, tomatoes, apple, soybean) and environmental allergens (bacteriofagoides, graminaceae, parietaria, trees, molds, pollens and animal epithelium, yeasts), drugs, solvents, and dyes
2. Normal total IgE, IgG, and IgA
3. Normal white blood cell count, blood chemistry, urinalysis, and serum complement levels (C₃ and C₄)
4. Fecal tests for yeasts, ova, and parasitic diseases.

Serology Measurements and CD Diagnosis. Concentrations of serum anti-transglutaminase (anti-tTG) IgG and anti-endomysium (EmA) IgA antibodies were assessed in all subjects. Anti-tTG antibodies were assessed by enzyme-linked immunosorbent assay (Eurospital, Trieste, Italy); titers above 7 arbitrary units/ml were considered positive, as suggested by the producer. EmA antibodies were detected by indirect immunofluorescence on sections of monkey esophagus (Eurospital, Trieste); positive staining of the endomysium around the smooth muscle fibers was judged as positive. In cases which proved to be positive to one or both serological tests, diagnosis was confirmed by means of histology on biopsy samples taken in the distal duodenum during an upper gastrointestinal endoscopy. The difference in the proportion of antibody-positive subjects between groups was assessed by Fischer's exact test.

RESULTS

Table 1 lists the demographic and serological characteristics of the study subjects. One of the 80 (1.25%) patients with ICU was positive to both anti-tTG and EmA. Histology confirmed the diagnosis of CD, showing subtotal villous atrophy. Another patient showed anti-tTG IgG in the borderline range (between 5 and 7 arbitrary units/ml) but negative EmA; however, duodenal histology excluded current CD in this patient. Among the blood donor group, 1 subject of 264 (0.38%) was found to be affected by CD. The prevalence of CD was not statistically different between patients and controls. Based on a baseline preva-

lence of CD antibody seropositivity of 1.5% in a European population (4), we calculated that our sample would give us the possibility to detect a clinically highly meaningful 6.2 relative risk of being CD-positive among ICU patients as opposed to controls, with an 80% power and a two-sided α level of 0.05.

DISCUSSION

The pathogenesis of ICU has been related to idiosyncratic or allergic reactions to drugs, food, or other environmental antigens or to some common chronic infections (e.g., *H. pylori*) (1, 2). However, evidence-based medicine does not fully support these theories. The most plausible pathogenic mechanism for ICU remains autoimmunity (1, 2). ICU has been associated with autoimmune disorders (in particular, autoimmune thyroiditis) (1); moreover, 35–40% of ICU patients have a circulating IgG antibody directed against the α subunit of the IgE receptor. An additional 5–10% have antibodies against the α subunit of IgE. IgEs are able to activate basophils and mast cells to release histamine, and complement fixation augments histamine release by formation of C5a anaphylatoxin (1).

On the other hand, CD is considered an inflammatory disorder with secondary autoimmune reactions. Autoimmune disorders are found 10 times more often in patients with CD than in the general population (3). In the present study, we found no association between ICU and celiac seropositivity. It should be reinforced that our sample size was powered to show an effect size corresponding to a relative risk increase for CD of six times, which would have a certain clinical meaning and would prompt testing for CD in patients with ICU. However, based on these data one cannot exclude a weaker, though significant, association. Some authors have reported cases of patients affected by ICU in which a diagnosis of CD was made and a gluten-free diet was associated with the disappearance of the cutaneous disease (7, 9–11). In a series of 32 children with ICU and without symptoms and signs of malabsorption syndrome, Meneghetti *et al.* found that 3 of them were affected by CD (anti-tTG antibody positive), and ICU manifestations improved after a gluten-free diet (12). Thus, an autoimmune reaction triggered by gliadin or by other unknown antigens has been proposed as a link between ICU and CD (11, 12).

To the best of our knowledge, the present is the only epidemiologic study assessing the prevalence of CD in a population of adult ICU patients. It shows that patients with ICU are as likely as normal controls to be found positive for CD antibody markers. The prevalence of CD marker positivity in our control group of blood donors resembles the prevalence in the general population in Europe, in

TABLE 1. DEMOGRAPHIC AND SEROLOGICAL CHARACTERISTICS OF THE STUDY SUBJECTS

	<i>Idiopathic chronic urticaria</i> (n = 80)	<i>Controls</i> (n = 264)
Age (mean $\pm$ SD)	48 $\pm$ 18	45 $\pm$ 16
Males	22	72
Anti-tTG	1	1
EMA-positive	1	1

whom 1 in 120 to 300 individuals are found to be positive according to different studies (3–5).

Although a possible pathophysiologic link between the two diseases remains, ICU patients do not seem to bear a greater risk for CD compared to the general population. These preliminary data remain to be confirmed by a larger epidemiological study, possibly assessing the prevalence of CD in the subgroups of ICU with and without α subunit IgE or IgE receptor autoantibodies.

REFERENCES

1. Kaplan AP: Clinical practice. Chronic urticaria and angioedema. *N Engl J Med* 346:175–179, 2002
2. Greaves MW: Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol* 3:363–368, 2003
3. Green PH, Jabri B: Coeliac disease. *Lancet* 362:383–391, 2003
4. Maki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, Ilonen J, Laurila K, Dahlbom I, Hansson T, Hopfl P, Knip M: Prevalence of Celiac disease among children in Finland. *N Engl J Med* 348(19):2517–2524, 2003
5. Farrell RJ, Kelly CP: Celiac sprue. *N Engl J Med* 346:180–188, 2002
6. Hautekeer ML, DeClerck LS, Stevens WJ: Chronic urticaria associated with coeliac disease. *Lancet* 1:157, 1987
7. Gallo C, Vighi G, Schroeder J, Strozzi M, Scibilia J, Colafrancesco M, Rota E, Ortolani C, Brusamolino R, Barberis M: Chronic urticaria atopic dermatitis and celiac disease. *Am J Gastroenterol* 87:1684, 1992
8. Levine A, Dalal I, Bujanover Y: Celiac disease associated with familial chronic urticaria and thyroid autoimmunity in a child. *Pediatrics* 104:e25, 1999
9. Farkas H, Visy B, Fekete B, Karadi I, Kovacs JB, Kovacs IB, Kalmar L, Tordai A, Varga L: Association of celiac disease and hereditary angioneurotic edema. *Am J Gastroenterol* 97:2682–2683, 2002
10. Mery A: Celiac disease presenting as urticaria. *Allergy Asthma Proc* 25(2):97–99, 2004
11. Candelli M, Nista EC, Gabrielli M, Santarelli L, Pignataro G, Cammarota G, Gasbarrini G, Gasbarrini A: Celiac disease and chronic urticaria resolution: a case report. *Dig Dis Sci* 49:1489–1490, 2004
12. Scala E, Giani M, Pirrotta L, Guerra EC, Guerra EC, De Pita O, Puodu P: Urticaria and adult celiac disease. *Allergy* 54:1008–1009, 1999