

Educational Clinical Case Series

Chronic urticaria and autoimmunity in children

Chronic urticaria (CU) is a common long-lasting skin disease characterized by widespread, transient wheals occurring daily or almost daily for at least 6 wk. In most of patients no apparent cause is identifiable (1, 2). It is now established that 30–50% of patients with chronic idiopathic urticaria (CIU) known as chronic autoimmune urticaria (CAU) have circulating autoantibodies directed against epitopes in the α -chain of the high-affinity receptor (Fc ϵ RI α) or against IgE (3,4). Recently it has been shown that in patients with severe CIU the intradermal injection of autologous serum elicits a wheal-and-flare response and mast cell degranulation (2). In clinical practice, a positive autologous serum skin test (ASST) has been used as a proxy for the measurement of functional autoantibodies to Fc ϵ RI, and it is assumed to be suggestive of an autoimmune pathogenesis of urticaria (4).

Only few studies are performed in children about the prevalence, laboratory and clinical characteristics of CAU. In previous studies, the majority of clinical and laboratory parameters examined to define the severity of urticaria showed no significant difference between patients with a wheal-and-flare response to autologous-serum skin test and patients with a negative response (4, 5). There are miscellaneous causes and disease associations with CU, which have no discernable common mechanisms. For example, autoimmune thyroid disease has been associated with CU in adults but rarely in children (6, 7). Also the role of *Helicobacter pylori* infection in CU is still a matter of debate, although the association between CU and *H. Pylori* has been found by some research groups (8, 9).

The aim of our study was to verify if there were any significant clinical and laboratory differences between patients with positive and with negative autologous-serum skin test.

Methods

A total of 40 consecutive patients (28 girls and 12 boys; median age 8.85; range, 3–17 yr) who are

admitted with CU between 1 January 2006, and 31 January 2007, to our University hospital, a tertiary center, defined as recurrent, short-lived wheal with or without angioedema and occurring more than 6 wk, were enrolled in the study. None was taking steroids or immunosuppressive therapy for at least 3 months before investigation. Anti-histamine therapy was stopped at least 2 wk before skin testing was performed and serum sample collected.

Medical history was recorded, and physical examination was performed. Skin prick tests with inhalant (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, birch pollen, hazel pollen, olive pollen, grass pollen mix [Cocksfoot, rye-grass timothy meadow grass, sweet vernal grass, oat grass, wild oat, meadow fescue, bent grass, Yorkshire fog Bermuda grass, bromus], mugwort pollen, stinging nettle pollen, ragweed pollen, fat hen pollen, wall pellitory pollen, cat and dog epithelia, latex, *Cladosporium*, *Aspergillus* and *Alternaria*) and food allergens (egg, fish, meat, fruits, legumes, peanut, hazelnut, nutmeg, milk, sesame, potato, tomato and soy); and provocation tests for physical urticaria (skin stroking for dermatographism, ice cube test for cold urticaria, exercise and hot bath provocation for cholinergic urticaria, pressure provocation for pressure urticaria) were carried out to diagnose allergic and physical urticaria. To investigate the other causes of CU, the patients underwent additional laboratory examinations (10), including the following: (i) blood tests for complete blood count, erythrocyte sedimentation rate, blood chemistry, liver function tests, serum levels of complement C3, C4 and C1 inhibitor, free thyroxine, thyroid stimulation hormone, serum total IgE; (ii) autoimmune panel (antinuclear antibody, antithyroid peroxidase antibodies, antithyroglobulin antibodies); (iii) infective panel (hepatitis surface antigen, antibody titers for hepatitis B and C virus, urine analysis and culture, throat culture, *H. pylori* IgG antibodies, microscopic investigation of stool for parasites ova).

ASST

All children underwent ASST. ASST was performed while the urticaria was active. The skin test technique, as previously defined by Sabroe et al. (2), was performed as follows: Venous blood was taken into sterile glass tubes without clotting accelerator and allowed to clot at room temperature for 30 min. Serum was separated by centrifugation at 500 *g* for 15 min. Fifty microliters of autologous serum, 0.9% sterile saline (negative control) and histamine (10 µg/ml, positive control) were injected into the dermis of the volar forearm at gaps of 5 cm between injecting sites. Wheal and flare responses were evaluated at 30 min, and previously determined parameters of the ASST with optimal sensitivity and specificity were used to define test positivity: the ASST response was taken to be positive when the serum-induced wheal had a diameter at least 1.5 mm greater than the saline-induced wheal. All ASSTs were performed by a single investigator.

Assessment of CU Activity

The clinical details we noted were the duration in months of the urticaria, the duration (greater than or less than 24 h) of individual urticarial wheals and their distribution. Moreover, the number and size of the wheals and severity of the itching were scored. CU activity was monitored using the urticaria activity score (UAS) according to the EAACI/GA2LEN/EDF guidelines (11) (Table 1). The UAS consisted of the sum of the wheal number score and the itch severity score.

Forty children in the same sex and age group who were treated in our hospital with diseases such as upper respiratory tract infection, pneumonia and gastroenteritis and addressed to outpatient clinic for routine control and without a history of wheezing or any other recurrent or chronic airway or inflammatory disease served as controls. These children had no parental history

of atopy or inflammatory disease. ASST was performed in all children in the control group. Other tests were only performed as needed for their medical situation.

The study was approved by the Ethics Committee of the Istanbul University Istanbul Medical Faculty.

Statistical analysis was performed by Mann–Whitney, χ^2 and Fisher's exact tests using the spss 12.0 software program (SPSS Inc, Chicago, IL, USA). A *p*-value <0.05 was considered significant.

Results

The extensive work-up allowed us to establish a cause for CU in 13 of 40 children (32.5%): physical urticaria (*n* = 6; 15%) and allergic urticaria (*n* = 7; 17.5%) if skin prick tests with inhalant and/or food allergens were positive and response to an elimination effort was useful. The remaining 27 of 40 patients (67.5%) are divided into the following two diagnostic groups: (i) CIU (*n* = 20 [50%]; 13 women [65%]; median age, 8.95 yr) if all of the aforementioned clinical and laboratory findings including ASST were within normal range. (ii) CAU (*n* = 7 [17.5%]; 5 women [71.4%]; median age, 7.43 yr) if ASST was positive.

A familial history of atopic diseases was recorded in five of seven patients with allergic urticaria and 2 of 20 patients with CIU. Three patients in allergic urticaria group had a positive personal history for asthma. Also a familial history of CU was recorded in three patients with CIU. The physical examinations of including height and weight measurements were normal in all of the patients except their urticarial lesions and/or angioedema.

None of the 40 patients had a positive test for ANA or had high sedimentation rate. The infective panel (hepatitis surface antigen, antibody titers for hepatitis B and C virus, urine analysis and culture, throat culture, microscopic investigation of stool for parasites ova, except *H. pylori* IgG antibodies) were negative in all patients.

ASST was positive in seven (25.9%) of 27 children in whom no apparent cause of urticaria was identified. ASST was found negative in all patients with physical and allergic urticaria, also in healthy controls.

There was no significant differences between patients with CAU and CIU as to the duration of symptoms, urticaria activation scores, age, gender and median serum IgE levels (Table 2). The prevalence of angioedema was higher in

Table 1 Chronic urticaria activation score

Score	Number of wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21–50 wheals/24 h)	Moderate
3	Intense (>50 wheals/24 h)	Intense

Sum of score: 0–6.

Pruritus: none – no pruritus; mild – pruritus, not affecting daily life; moderate – pruritus affecting daily life; intense – pruritus modifying daily life and daily activities.

Table 2 Characteristics of patients with chronic autoimmune urticaria (CAU) vs. chronic idiopathic urticaria (CIU)

	CAU (n = 7)	CIU (n = 20)	p
Age, yr	7.43 ± 3.952	8.95 ± 3.53	0.291
Female/male	5/2	13/7	0.571
Angioedema	6/7 (85.7%)	12/20 (60%)	0.224
Urticaria activity score	3.86 ± 1.07	3.20 ± 0.95	0.135
Duration of symptoms, (months)	19.29 ± 34.736	13.85 ± 11.0	0.466
Serum IgE (IU/ml)	149.0714 ± 154.05584	77.7550 ± 55.3362	0.128
Thyroid autoimmunity	1 (14.3%)	3 (15%)	0.731
<i>Helicobacter pylori</i> IgG positivity	0 (0%)	6 (30%)	0.131

autoimmune group (87.5%) compared to patients in CIU (60%), even if this result was again not statistically significant.

Anti-thyroid autoantibodies were detected in four patients, only one of them was in the autoimmune group and the others were in the idiopathic group. *Helicobacter pylori* IgG antibodies was detectable in 6 of the 20 patients with CIU; but none of the autoimmune group had *H. pylori* antibody positivity. Although statistically insignificant, we found that two patients with physical urticaria and one patient with allergic urticaria had positive *H. pylori* antibodies. Anti-thyroid antibodies were not detected in patients with allergic and physical urticaria.

The approach to CU and diagnostic groups in patients enrolled in the study is shown in Fig. 1.

Discussion

CU is defined as widespread, transient (< 24 h) wheals occurring daily or almost daily for at least 6 wk (2). Although CU is an infrequent disease of the childhood, our understanding of its pathogenesis, classification and management is increasing (12).

Most of the series involving children with CU are reported in a median age of 6–11 yr. But the range is relatively wide, sometimes beginning from the first years of life to adolescence (4, 10). As in other studies, we have observed that small children are relatively rare and protected in some way. This may partly be explained with the concept of the pathogenesis of autoimmunity and allergy. The development of disease might require the action of environmental factors on the genetically predisposed host. Environmental triggers may be more prominent with the growing age and the development of the immune system.

Studies in adults and children have demonstrated that antibodies against the FcεRIα are detectable in 25–40% and 30–50% of patients

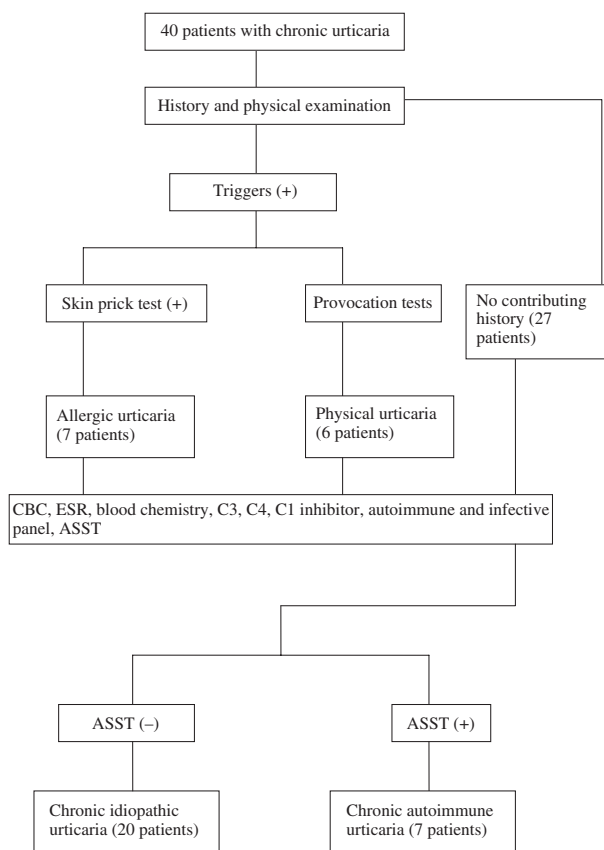


Fig. 1. Flow chart: approach to chronic urticaria in patients enrolled in the study.

with CIU, respectively (1, 4, 13). The mast cell-specific histamine-releasing assay (HRA) allows the *in vitro* detection of FcεRIα, anti-IgE or other histamine-releasing factors (2). A correlation between the presence anti-FcεRIα and anti-IgE antibodies and positive ASST was documented (2, 14). Brunetti et al. (4) found a good concordance between ASST and HRA, with sensitivity and specificity of the ASST for detecting autoantibodies of 78% and 85%, greater than figures reported in adults (2). Therefore, ASST which is cheap and easy to perform, can be used as a predictive clinical test to diagnose CAU, especially in places where basophil histamine-releasing test is not available (4).

In the present study, we have demonstrated a 25.9% prevalence of ASST among CIU patients, which is much lower than reports from Western countries. This can be because of false negative results of the ASST. A negative ASST may reflect the injection of the autologous serum in a refractory site secondary to a recent wheal (2). Also there is a concern about the false negative results because of degradation of histamine releasing factors while the serum is being

processed (15). But it is possible that some genetic factors can influence the positivity of ASST in patients with CIU. In previous studies with Asian patients with CIU, Godse (16) and Kulthanan (17) found a ASST positivity in 26.67% and 24.5% of cases, respectively. The most convincing evidence of a genetic predisposition for autoimmune disease in CIU comes from studies of major histocompatibility complex class II association. Strong positive HLA DR4 and HLADQ8 allele association suggests genetic component in the pathogenesis of CU (18).

In the present study, we do not find any ASST positivity in healthy control group. Also, previous studies found an absence or rarely positive ASST in healthy control subjects (1, 2). However, Mari and Guttman-Yassky (19, 15) reported a positive ASST in 45% and 40.5% of healthy control individuals, respectively. But the ASST positivity in these studies was not confirmed with basophil HRAs.

Previous studies determining the clinical differences between patients with and without autoantibodies were performed. Sabroe et al. (20) showed that adult patients with autoantibodies had more wheals, a wider distribution of wheals, higher itch scores, more systemic symptoms, and lower serum IgE levels than patients without antibodies. But Nettis et al. (5) found no significant differences in wheal number and size, itching scores and mean duration of urticaria between adult patients with or without response to ASST. Brunetti et al. (4) compared the clinical and laboratory features of children with CAU and CIU, but they could not find any difference between the autoimmune and non-autoimmune groups, except for monocyte count and serum IgM. In the present study, we could not show any difference in age, gender, duration of symptoms, symptom scores and mean serum IgE levels between patients with or without response to ASST. So, we believe that ASST positivity cannot be used alone to predict the severity of CU.

Reports of an increased prevalence of antithyroid autoantibodies among patients with CU in different populations have led to recommendations for the testing of all patients with CU for autoimmune thyroid disease (7). The prevalence in adult series ranges from 14% to 33% (6, 7, 21), which is much higher than that in children with CIU. Levy et al. (6) reported a 4.3% prevalence of autoimmune thyroiditis in children with CIU, which is higher than the prevalence reported before. In the present study, we found a 14.8% prevalence of thyroid autoimmunity in patients with CIU, less than reported in adults but higher

than that reported in children before. The likelihood of having an autoimmune disease increases with age and also thyroid autoimmunity which is an evolving process may be manifested several years after the appearance of CU. These factors can explain generally the low prevalence in thyroid autoimmunity in children. Also in previous studies a higher prevalence of thyroid autoimmunity is reported in patients with CAU than that in patients with CIU (7, 21). Although statistically insignificant, we found a higher prevalence of antithyroid antibodies in non-autoimmune group. In fact this finding confirms other authors' data (5, 22), but it can also be because of false negative results of the ASST explained before in the text.

The mechanism whereby thyroid autoimmunity is associated with urticaria is poorly understood. Thyroid stimulation by thyroid-stimulating hormone (TSH) drives glandular activity and potentially exacerbates inflammation. The inflammation, caused by the presence of autoantibodies, disrupts the normal architecture of the gland and leads to cellular disarray and the release of sequestered antigens, which are perceived as non-self and induce a low-grade autoimmune response. Products of this autoimmune response such as thyroid protein immune complexes activate classical complement pathway, leading to generation of C3a and C5a which cause degranulation of mast cells (23). Bakos et al. (21) found an increased incidence of *H. pylori* infection in their CU patients with thyroid autoimmunity. They suggested that *H. pylori* might produce an antibody response that cross-reacts with thyroid peroxidase because of molecular similarity. Magen et al. (24) found a higher prevalence of antithyroid antibodies in *H. pylori* positive CAU group than *H. pylori* positive CIU group. In our study, similar results like in thyroid autoimmunity were obtained and all patients with *H. pylori* antibody positivity were found in the non-autoimmune group.

The role of *H. pylori* infection in the etiology of CIU is still controversial. While several authors found a higher prevalence of *H. pylori* infection in CIU (8, 9) and demonstrated that *H. pylori* eradication therapy associated with the remission of CU, suggesting a possible role in etiology (24), others found the opposite result (25). Also few studies demonstrated a higher prevalence of ASST positivity in *H. pylori* antibody positive patients (26), whereas several authors could not find any correlation between *H. pylori* infection and autoimmune urticaria (21). Nettis et al. (5) found *H. pylori* IgG positivity in 36 of the 102 patients with CIU.

Although statistically insignificant they found a higher prevalence of *H. pylori* infection in non-autoimmune group. In the present study, we found *H. pylori* antibody positivity in 6 of the 20 patients with CIU; but none of the autoimmune group had *H. pylori* antibody positivity. Although statistically insignificant, we found that two patients with physical urticaria and one patient with allergic urticaria had *H. pylori* infection. There are few studies in the literature about the prevalence of *H. pylori* infection in physical/allergic CU patients. *Helicobacter pylori* infection might trigger the production of IgE antibodies or cause an inflammation in gastrointestinal tract, which might facilitate the absorption of antigens (26).

There are some case reports of an association between CU and celiac disease, which may improve on a gluten-free diet (27, 28). It is recommended to consider coeliac disease in children with refractory CU (28). In our study, because of absence of cases refractory to treatment with antihistamines, the antiendomysial and transglutaminase antibodies of patients were not assayed.

Infection has been included in most reviews of CU. Parasitic infection was the classic one described, but successful eradication rarely resulted in remission of the hives (23). In the present study, we do not find any parasitic infection as a cause of CU. Also, there are previous studies that found a low rate of parasitemia in patients with CU (13). As a clear association between parasitemia and CU has not been established, this knowledge can prevent the over-investigation in patients with CU, unless there is an unexplained eosinophilia and a relevant history of travel abroad (29).

The low numbers of patients in different subgroups depending on etiology is the major limitation of this study. The other possible misleading factor is the absence of small children under 3 yr old in our series. Despite the increased production of autoantibodies during aging, the incidence of autoimmune disease does not increase with age (29). Our study could not be sufficient to highlight the frequency of CAU in the first few years of life.

Positive ASST was observed in 25.9% of patients with CIU which is less than reports from Western literature. It is not clear whether CAU with autoantibodies can be classified as an autoimmune disease. We observed no difference between children with CAU and CIU in mean serum IgE levels, UASs, duration of symptoms and incidence of angioedema. The lower prevalence of the patients with thyroid antibodies and

the absence of the patients with *H. pylori* positivity among ASST positive children, imply that mechanisms which may play a role in the induction of autoantibodies in CAU are different from those that may be involved in CIU. As the autoimmunity is an evolving process, long-term follow-up studies from infancy to adulthood are needed.

Gurkan Kilic¹, Nermin Guler¹, Ayse Suleyman¹, Zeynep Tamay¹

¹Division of Allergy and Chest Diseases,
Department of Pediatrics, Istanbul
Medical Faculty, Istanbul University, TURKEY

References

1. HIDE M, FRANCIS DM, GRATTAN CEH, HAKIMI J, KOCHAN JP, GREAVES MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993; 328: 1599–604.
2. SABROE RA, GRATTAN CEH, FRANCIS DM, BARR RM, KOBZA BLACK A, GREAVES MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; 140: 446–53.
3. GRATTAN CEH, FRANCIS DM, HIDE M, GREAVES MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991; 21: 695–704.
4. BRUNETTI L, FRANCAVILLA R, MINIELLO VL, et al. High prevalence of autoimmune urticaria in children with chronic urticaria. *J Allergy Clin Immunol* 2004; 114: 922–7.
5. NETTIS E, DAMBRA P, D'ORONZIO L, et al. Reactivity to autologous serum skin test and clinical features in chronic idiopathic urticaria. *Clin Exp Dermatol* 2002; 27: 29–31.
6. LEVY Y, SEGAL N, WEINTROB N, DANON YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; 88: 517–9.
7. O'DONNELL BF, FRANCIS DM, SWANA GT, SEED PT, KOBZA BLACK A, GREAVES MW. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 2005; 153: 331–5.
8. WEDI B, WAGNER S, WERFEL T, MANNS MP, KAPP A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998; 116: 288–94.
9. TEBBE B, GEILEN CC, SCHULZKE JD, BOJARSKI C, RADENHAUSEN M, ORFANOS CE. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol* 1996; 34: 685–6.
10. THOMAS P, PERKIN MR, RAYNER N, et al. The investigation of chronic urticaria in childhood: which investigations are being performed and which are recommended? *Clin Exp Allergy* 2008; 38: 1061–2.
11. ZUBERBIER T, BINDSLEV-JENSEN C, CANONICA W, et al. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006; 61: 316–20.
12. LARA-CORRALES I, BALMA-MENA A, POPE E. Chronic urticaria in children. *Clin Pediatr (Phila)* 2009; 48: 351–5.
13. DU TOIT G, PRESCOTT R, LAWRENCE P, et al. Autoantibodies to the high-affinity IgE receptor in children with chronic urticaria. *Ann Allergy Asthma Immunol* 2006; 96: 341–4.

14. FUSARI A, COLANGELO C, BONIFAZI F, ANTONICELLI L. The autologous serum skin test in the follow-up of patients with chronic urticaria. *Allergy* 2005; 60: 256–8.
15. GUTTMAN-YASSKY E, BERGMAN R, MAOR C, MAMORSKY M, POLLACK S, SHAHAR E. The autologous serum skin test in a cohort of chronic urticaria patients compared to respiratory allergy patients and healthy individuals. *J Eur Acad Dermatol Venereol* 2007; 21: 35–9.
16. GODSE KV. Autologous serum skin test in chronic urticaria. *Indian J Dermatol Venereol Leprol* 2004; 70: 283–4.
17. KULTHANAN K, JIAMTON S, THUMPIMUKVATANA N, PINKAEW S. Chronic idiopathic urticaria: prevalence and clinical course. *J Dermatol* 2007; 34: 294–301.
18. O'DONNELL BF, NEILL CM, FRANCIS DM, et al. Human leucocyte antigen class II associations in chronic urticaria. *Br J Dermatol* 1999; 140: 853–8.
19. MARI A. Allergy-like asthma and rhinitis. A cross-sectional survey of a respiratory cohort and a diagnostic approach using the autologous serum skin test. *Int Arch Allergy Immunol* 2004; 133: 29–39.
20. SABROE RA, SEED PT, FRANCIS DM, BARR RM, BLACK AK, GREAVES MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcepsilonRI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999; 40: 443–50.
21. BAKOS N, HIGHLANDER M. Comparison of chronic autoimmune urticaria with chronic idiopathic urticaria. *Int J Dermatol* 2003; 42: 613–5.
22. VERMEULEN C, MATHIELIER-FUSADE P, ROUQUETTE AM, BAYROU O, PECQUET C, LEYNADIER F. Chronic urticaria, thyroiditis and autologous serum test. *Ann Dermatol Venereol* 2003; 130: 1115–8.
23. SCHOCKET AL. Chronic urticaria: pathophysiology and etiology, or the what and why. *Allergy Asthma Proc* 2006; 27: 90–5.
24. MAGEN E, MISHAL J, SCHLESINGER M, SCHARF S. Eradication of *Helicobacter pylori* infection equally improves chronic urticaria with positive and negative autologous serum skin test. *Helicobacter* 2007; 12: 567–71.
25. HOWDEN C. No evidence for an association between *H. pylori* and idiopathic chronic urticaria. *Dig Dis Sci* 1999; 44: 485–6.
26. HIZAL M, TUZUN B, WOLF R, TUZUN Y. The relationship between *Helicobacter pylori* IgG antibody and autologous serum test in chronic urticaria. *Int J Dermatol* 2000; 39: 443–5.
27. GABRIELLI M, CANDELLI M, CREMONINI F, et al. Idiopathic chronic urticaria and celiac disease. *Dig Dis Sci* 2005; 50: 1702–4.
28. CAMINITI L, PASSALACQUA G, MAGAZZU G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol* 2005; 16: 428–32.
29. POWELL RJ, DU TOIT GL, SIDDIQUE N, et al. BSAIC guidelines for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2007; 37: 631–50.
30. WEKSLER ME, SZABO P. Aging and the immune system. In: RICH RR, FLEISHER TA, KOTZIN BL, SCHROEDER HW, eds. *Clinical Immunology, Principles and Practice*. London: Mosby, 2001: 41.1–8.