Original Article

Low B_{12} levels in chronic idiopathic urticaria

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Summary. Recent studies suggest that autoimmune mechanisms may be involved in the etiology of chronic idiopathic urticaria (CIU). There is a higher prevalence of B_{12} deficiency in autoimmune diseases and possibly in gastric Helicobacter pylori (H. pylori) infection. The frequency of B_{12} deficiency in CIU is unknown.
Our *objective* in this study was to determine the prevalence of B_{12} deficiency in patients with CIU and also its relationship to gastric H. pylori infection and serologic markers of autoimmunity in these groups.
Thirty-three patients with CIU and 27 healthy controls were included in the study. Serum vitamin B_{12} levels, H. pylori infection and serological markers of autoimmunity (anti-thyroglobulin, thyroid microsomal, gastric parietal cell and antinuclear autoantibodies) were investigated. H. pylori infection was determined according to serology and gastric biopsy in 19 patients, serology and urea breath test in 4 patients and serology alone in the remaining 10 patients.
Serum B_{12} levels were below the normal reference range in 11/33 (33.3%) patients with CIU. The mean serum B_{12} levels among patients with CIU and the controls were 281±127.5 pg/ml and 465.1±140.3 pg/ml (p=0.0001), respectively. Anti-thyroid antibodies were positive in 6 of 11 patients (54.5%) with low B_{12} levels, but only in 4 of 27 (14.8%) healthy controls (p=0.019). Anti-GPC antibodies were positive in 4 of 11 (36.4%) patients with CIU and low B_{12} levels, but only in 2 of 27 (7.4%) healthy controls (p=0.047). In CIU patients, there was no difference in the frequency of IgG H. pylori antibodies between those with low B_{12} levels and normal B_{12} levels. Among the 19 patients who had been performed gastric endoscopy, 15 patients (78.9%) had chronic antral gastritis, 2 patients (10.5%) had atrophic gastritis and there were normal findings in 2 patients (10.5%).
In conclusion, serum B_{12} levels were found to be below the normal reference range in 33% of the patients with CIU. An association between low B_{12} levels and H. pylori could not be shown. The higher frequency of anti-thyroid and anti–GPC antibodies in patients with low B_{12} levels suggest that low B_{12} levels in CIU may be autoimmune in nature.

Key words: Chronic idiopathic urticaria, vitamin B_{12} deficiency, autoimmunity, anti-thyroid antibodies, gastric. parietal cell antibodies, Helicobacter pylori.

Introduction

Chronic urticaria (CU) is a common clinical condition characterized by occurrence of daily itchy wheals that last at least 6 weeks. In the majority of the patients, the disease is considered to be idiopathic with no identifiable etiology [1]. However, mast cell degranulation and histamine release are thought to be of central importance. Autoantibodies reactive against the α subunit of the high affinity IgE receptor (FcεRIα) and/or the IgE itself are present in the serum in 30 to 50% of the patients with chronic idiopathic urticaria (CIU) [2, 3]. These autoantibodies are responsible for mast cell degranulation and a cascade of reactions resulting in wheal formation in some patients with CIU [4]. Mast cell degranulation by autoantibodies appears to be augmented by complement activation [5].

Studies have shown a relationship between urticaria and thyroid autoimmunity. Screening for thyroid autoimmunity by testing for thyroid microsomal and thyroglobulin antibodies is recommended in patients with urticaria. Antithyroid antibodies are thought not to be pathogenic, but serving as indicators of autoimmunity [6].

Patients with autoimmune disorders have a higher prevalence of B_{12} deficiency when compared with the general population. The incidence of B_{12} deficiency in patients with autoimmune thyroid diseases and vitiligo has been reported to be up to 9 times more common than in the normal population [7]. The association of B_{12} deficiency and autoimmune disorders has been attributed to the coexistence of anti-intrinsic factor and gastric parietal cell (GPC) antibodies with the autoimmune antibodies responsible for the underlying autoimmune disorder [7]. The prevalence of B_{12} deficiency in CIU is unknown.

Coexistence of *H. pylori* infection with chronic urticaria is increasingly being reported although a causative relationship has not been firmly established [8, 9]. *H. pylori* infection has also been reported to cause B_{12} deficiency by inducing severe food-cobalamin malabsorbtion or by inducing autoantibodies that react with gastric parietal cell canaliculi due to the molecular similarities between the H+K+ ATP'ase pump of the gastric parietal cell and the *H. pylori lipopolysaccharide* [10-12]. Therefore, if not treated gastric *H. pylori* infection can cause parietal cell loss and ultimately chronic atrophic gastritis and pernicious anemia [13, 14].

In this study, we determined serum B_{12} levels in patients with CIU and addressed the relationship between low B_{12} levels and the presence of autoantibodies or *H. pylori* infection.

Material and Methods

Patients with chronic urticaria, defined as recurrence of urticarial symptoms at least twice a week for more than 6 weeks were identified in the year 2002 registry of Immunology and Allergy outpatient clinic. Thirty-three patients, who were diagnosed as having CIU after exclusion of patients with drug, food, infection and exercise related urticaria, and signed an informed consent, were included to the study. Patients with urticarial vasculitis confirmed by histology were also excluded. The mean age was 42 years (range 18-63). There were 29 females and 4 males. As a control group, 27 sex and age-matched healthy adults were also included in the study. The mean age was 39.2 years (range 26-55). There were 20 females and 7 males in the control group. The patient and control group characteristics are shown in Table 1.

Table 1. Characteristics of patients with CIU and control group.

	CIU	Control	P
Sex (m/f)	4/29	7/20	0.175†
Mean age in years	42	39.2	0.237‡
(range)	(18-63)	(26-55)	
Mean B_{12} levels±SD pg/ml	281.4±127.5	464.9±140.3	0.0001‡
(range)	(73-529)	(290-880)	
H. pylori IgG (% positive)	(75.8%)	(51.9%)	0.055†
(positive/negative)	25/8	14/13	

† Chi-square test

‡ T-test

For determination of vitamin B_{12} levels, blood samples were collected from the patients and the controls and allowed to clot adequately before centrifugation. Within two hours of centrifugation, 500 ml of cell-free serum was transferred to a tightly closed storage tube. The serum samples were stored at room temperature for no longer than 8 hours. Serum B_{12} levels were measured by a competitive immunoenzymatic binding assay (Beckman Access Immunoassay System, USA). Manufacturer's recommended normal ranges for serum B_{12} levels were between 180 pg/ml and 914 pg/ml.

Serum folic acid assays were performed using Roche Elecsys 2010 and Modular Analytics E170 immunassay analysers. This system employs a competitive test principle using natural folate binding protein specific for folate. Using this kit, the normal reference range for serum folate is 4.2-19.9 ng/ml.

H. pylori infection was determined by serum IgG anti-*H. pylori* antibody measurement, endoscopic biopsy and urea breath test. Serum anti-*H. pylori* IgG antibodies were detected by using a commercial ELISA kit (CAPTIA H. Pylori IgG ELISA, Trinity Biotech, USA) according to the manufacturer's instructions. An upper gastrointestinal endoscopy was performed in 19 of the 33 patients who had positive H. pylori serology and also authorised the procedure. During endoscopy, three mucosal biopsies were taken from the antrum and corpus regions of the stomach each. Two of the biopsy specimens from each region were evaluated histologically with hematoxylin-eosin and toluidine blue staining. The other biopsies were used for the urease test. The diagnosis of H. pylori infection was made when the IgG anti-H. pylori antibodies were found to be positive in combination with a positive rapid urease test or histological evidence of H. pylori infection in the gastric biopsy or in the presence of a positive urea breath test.

To assess anti-thyroglobulin (anti-T) and anti-thyroid microsomal (anti-M) antibodies, patients' sera were studied using a hemagglutination kit (Murex Diagnostic GmbH, Germany). Titers higher than 1/160 were considered positive. GPC antibodies were quantified on rat stomach tissue substrate sections using immunofluorescence technology (Zeus Scientific, Inc, Germany). Fluorescence detection at 1/40 or higher titrations of the patients sera was considered positive. Intrinsic factor antibodies were measured by using the ELISA technology (Genesis Diagnostics, UK). Antinuclear autoantibodies (ANA) were also determined and quantified using the immunofluorescence technology (Binding Site, HEP-2 Slides, UK). Titers 1/80 or higher were considered positive.

Statistical Analysis

The chi-square test when appropriate was used for comparison of the frequency data. The t test was used to compare variables between groups. A p-value <0.05 was considered statistically significant.

Results

The serum B_{12} levels were between 73 pg/ml and 529 pg/ml in the 33 patients with CIU and 290 pg/ml and 880 pg/ml in the 27 healthy controls (Table 1). The mean serum B_{12} levels in patients with CIU and controls were 281.4±127.5 pg/ml and 464.9±140.3 pg/ml, respectively (p=0.0001) (Fig. 1). Serum B_{12} levels were

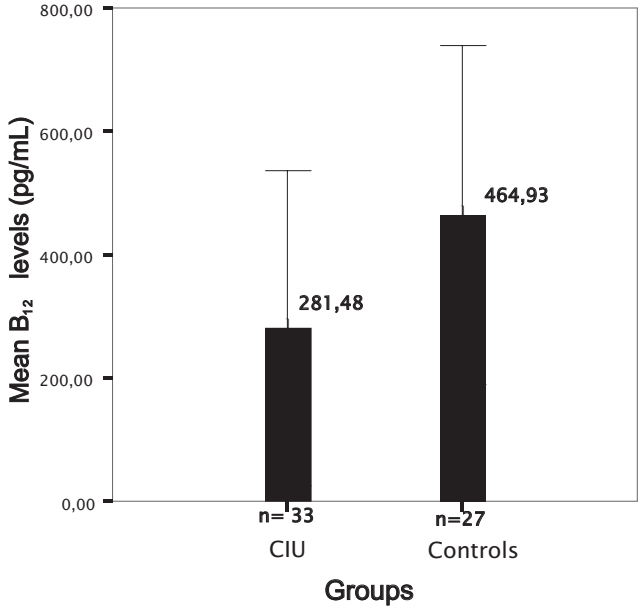

Figure 1. The mean serum B_{12} level in patients with CIU was significantly lower than that of the control group (p=0.0001).

Table 2. Serum B_{12} and folic acid values in CIU patients with low B_{12} levels

Patients no	B_{12} values (180-914 pg/ml)	Folic acid values (4.2-19.9 ng/dl)
1	165	4.5
2	169	7.9
3	165	6.5
4	155	5.6
5	150	6.9
6	117	7.3
7	73	5.6
8	108	5.8
9	170	6.1
10	134	5.6
11	137	4.6

below the normal reference range of 73-180 pg/ml in 11 of the 33 patients (33.3%) with CIU. In contrast, all of the healthy control subjects had serum B_{12} levels that were within the normal reference range (Table 1). The serum folic acid levels were within normal limits in all patients and controls. Folic acid levels in patients with low B_{12} levels are shown in Table 2. Intrinsic factor antibodies were studied in all patients with low B_{12} levels and found to be positive in only 2 (18%) patients.

Autoantibodies against thyroid tissue antigens, anti-GPC antibodies and ANA were positive in 11 (33.3%), 5 (15.2%) and 6 (18.2%) patients in the CIU group, and in 4 (14.8%), 2 (7.4%) and 1 (3.7%) individuals in the control group, respectively (Table 3). Although the autoantibodies were 2 to 5 times more common in the CIU patients than in the healthy controls, the differences between the two groups did not reach statistical significance.

Table 3. Autoantibodies in the CIU and the control group.

	CIU number positive/number tested	Control number positive/number tested	P†
Anti T-, -M	11/33 (33.3%)	4/27 (14.8%)	0.103†
Antibodies to GPC	5/33 (15.2%)	2/27 (7.7%)	0.361†
ANA	6/33 (20.8%)	1/27 (3.7%)	0.085†

†Fischer's Exact Test

Abbreviations. Anti-T, anti-thyroglobulin; anti-microsomal antigen; GPC, gastric parietal cell; ANA, antinuclear antibody.

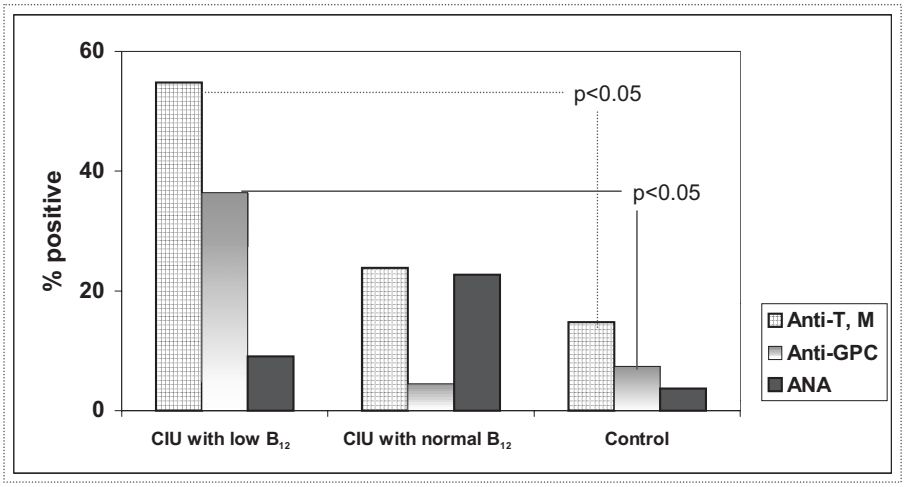

Figure 2. The anti-T, anti-M and anti-GPC antibodies were significantly more common in CIU patients with low B_{12} levels than in the healthy controls.

The groups who had normal and low serum B_{12} levels were compared with regard to the frequency of autoantibodies. Anti-T and -M antibodies were detected in 6 of the 11 patients (54.5%) with CIU and low serum B_{12} levels. In contrast, 4 of the 27 healthy controls (14.8%) and 5 of the 22 patients (22.7%) with CIU and normal B_{12} levels had detectable anti-T and –M antibodies. The difference between the CIU patients with low B_{12} levels and the healthy controls reached statistical significance (p=0.019) (Fig. 2). Similarly, anti-GPC antibodies were more common in the CIU patients with low B_{12} levels when compared to those seen in the CIU patients with normal B_{12} levels and in healthy controls [4 of 11 (36.4%), 1 of 22 (4.5%) and 2 of 27 (7.4%), respectively]. The anti-GPC antibodies were 5 times more common in the CIU patients with low B_{12} levels than in the healthy controls (p=0.047). The frequency of ANA was similar in patients with CIU and low B_{12} levels and healthy controls (Fig. 2).

The frequency of IgG H. pylori antibodies was not different between the CIU patients with low B_{12} levels, the CIU patients with normal B_{12} levels and the healthy controls. IgG H. pylori antibodies were positive in 8 out of 11 (72.7%), 17 out of 22 (77.3%) and 14 out of 27 (51.9%) individuals among the groups with CIU and low B_{12} levels, CIU and normal B_{12} levels and healthy controls, respectively.

An upper gastrointestinal system endoscopy was performed in 19 patients with CIU who had a positive IgG anti-H. pylori antibody test and gave permission for the procedure. Endoscopic biopsy showed gastric inflammatory changes in 17 (89.4%) patients. The endoscopy was unremarkable in 2 patients. Of the 17 patients, 15 (88%) had chronic antral gastritis and 2

Table 4. H. pylori infection, antibodies to GPC and B_{12} levels in patients with chronic antral gastritis and atrophic gastritis

	Atrophic gastritis n=2	Chronic antral gastritis n=15	P†
H. pylori infection	1 (50%)	12 (75%)	0.426
Antibodies to GPC	2 (100%)	1 (6.7%)	**0.022**
Low B_{12} levels	2 (100%)	4 (26.7%)	0.110

† Fischer's Exact Test

The diagnosis of H. pylori infection was made if IgG H. pylori antibodies were found to be positive in combination with a positive rapid urease test or histological evidence or H. pylori infection in gastric biopsy. GPC, gastric parietal cell.

(12%) had atrophic gastritis. *H. pylori* infection, defined as a positive IgG anti-*H. pylori* antibody test in combination with a positive rapid urease test or histological evidence of *H. pylori* infection in the gastric biopsy, was seen in 1 out of 2 patients with atrophic gastritis and in 12 out of 15 with chronic antral gastritis. The relationship between the histological findings and the frequency of anti-GPC antibodies is shown in Table 4. Both patients with atrophic gastritis had detectable anti-GPC autoantibodies, whereas only one patient (6.7%) with chronic antral gastritis had a positive anti-GPC autoantibody test ($p<0.022$). Four patients with chronic antral gastritis (26.7%) and both patients (100%) with atrophic gastritis had B_{12} levels below the normal reference range. The diagnosis of *H. pylori* infection was established in 4 patients by urea breath test.

Discussion

In this study, serum B_{12} levels were found to be below the normal reference range in 33.3% of the patients with CIU. In contrast, none of the healthy controls had low B_{12} levels. Interestingly, none of the patients with low B_{12} levels had hematological or neurological manifestations of B_{12} deficiency (data not shown). The study made sure that low B_{12} levels were not due to diet habits. None of the patients in the study was vegetarian or described a dietary restriction. The fact that all control subjects had normal B_{12} levels argues against the possibility that low levels in patients may be due to a technical error.

The reason for low B_{12} levels in some patients with CIU is unknown. Anti-GPC antibodies were detected with higher frequency in patients with CIU and low B_{12} levels than in healthy controls. Furthermore, pathological evidence of gastritis was shown in 6 out of 7(85.7%) patients with low B_{12} levels who underwent upper gastrointestinal endoscopy. Anti-GPC antibodies and gastritis are common findings also in pernicious anemia, an autoimmune disease considered to be the most common cause of B_{12} deficiency. In pernicious anemia, gastric parietal cells located in the corpus region of the stomach are destroyed by anti-GPC autoantibodies, while the antrum is spared. In our study, 2 of the 7 (28.5%) patients with CIU and low B_{12} levels had atrophic gastritis, a common finding in advanced pernicious anemia. However, the remaining 5 patients (71.5%) had chronic antral gastritis. Furthermore, intrinsic factor autoantibodies seen in approximately 60% of the patients with B_{12} deficiency, were detected only in 2 of the 11 patients (18%) with CIU and low B_{12} levels. These results suggest that different causative mechanisms operate in patients with CIU and low B_{12} levels. Chronic antral gastritis is a common finding in gastric *H. pylori* infection. All 4 patients with low B_{12} levels and antral gastritis in our study also had gastric *H. pylori* infection suggesting that antral gastritis in these patients may in fact be related to concomitant *H. pylori* infection. The data, however, do not support a causative role for *H. pylori* infection in the etiology of low B_{12} levels in patients with CIU as the overall prevalence of *H. pylori* was found to be the same in patients with low and normal B_{12} levels.

Food-cobalamin malabsorption, an entity characterized by inability to absorb food-bound cobalamin by a person normally capable of absorbing free cobalamin is another potential cause for B_{12} deficiency. The use of H2 antagonists, proton pump inhibitors and *H. pylori* infection are known to be associated with food-cobalamine malabsorption [15]. None of our patients were on H2 antagonist or proton pump inhibitor therapy. Serum markers of gastritis are not sensitive or specific enough to serve as a diagnostic substitute for direct testing of absorption in the diagnosis of food-cobalamine malabsorption [16]. Because we did not test for cobalamine malabsorption, we cannot exclude it as the cause of low B_{12} levels in our patients. However, in the absence of diarrhea and other gastrointestinal symptoms, the diagnosis of malabsorption is unlikely. The serum folic acid levels were found to be normal in all patients with CIU and controls. Therefore, B_{12} deficiency in CIU does not appear to be a surrogate for folic acid deficiency [17]. Excessive intake of vitamin C has also been shown to cause B_{12} deficiency. We found no evidence of vitamin C use in the patients with CIU and low B_{12} levels [18].

Interestingly, none of the patients with low B_{12} levels had hematological or neurological evidence of pernicious anemia (data not shown). Biochemical evidence of B_{12} deficiency in the absence of anemia is quite common, especially in the elderly [19]. Stabler et al. showed in their study that 44% of the patients with B_{12} deficiency were not anemic and another 36% had a mean cell volume ≤100 fL [20]. The reason for lack of anemia in some patients with B_{12} deficiency is unknown. It is possible that the onset of anemia and neurological symptoms may lag behind biochemical evidence of B_{12} deficiency. Considering the fact that the average patient presenting with symptomatic B_{12} deficiency is around 60 years of age and the mean age of our study population was 42, further follow up would be necessary to determine whether anemia would develop in the middle aged patients with CIU and biochemical B_{12} deficiency [7]. The patients with low B_{12} levels in this study were treated with B_{12} injections. Stabler and colleagues showed that a significant portion of the patients with biochemical evidence of B_{12} deficiency will have subtle clinical manifestations and will respond to treatment with B_{12} injections [20].

Although not completely understood, recent studies indicate that autoimmunity may be involved in the etiology of CIU at least in a subset of patients [1, 2]. There is a wide spectrum of autoimmune diseases associated with urticaria. Several studies and case reports

have shown a relationship between chronic urticaria and autoimmune diseases including Addison's disease, diabetes mellitus, primary sclerosing cholangitis, primary hyperparathyroidism, pernicious anemia and vitiligo [21-23]. Autoantibodies against the high affinity IgE receptor and/or IgE itself, which are common in patients with CIU as shown in several studies, are also found in other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, pemphigus vulgaris, bullous pemphigoid. But neither the patients with these autoimmune diseases did have CIU nor these autoantibodies antibodies appeared to be functional [4]. In our study, anti-thyroid, anti-GPC and ANA were detected 2 to 5 times more frequently in patients with CIU than in the control group. This observation supports the previous studies, which suggested an autoimmune basis to CIU.

An association between *H. pylori* infection and chronic urticaria has also been reported [8, 9]. The observation that eradication of *H. pylori* can lead to remission of urticaria symptoms suggest a causative role for *H. pylori* at least in some patients [24, 25]. In our study, IgG anti-*H. pylori* antibodies were found more frequently in patients with CIU than in healthy adults. However, the difference was not statistically significant (p=0.055). There was no difference in the frequency of anti-H. pylori antibodies between the CIU patients with low B12 levels and normal B_{12} levels (p=1). Therefore, a role for the *H. pylori* infection in the etiology of low B_{12} levels in the CIU patients could not be established.

In conclusion, this study disclosed that 33.3% of patients with CIU have serum B_{12} levels that are below the normal reference range. The finding that anti-GPC, anti-T and anti-M antibodies are more frequent in patients with CIU and low B_{12} levels may be suggesting an autoimmune etiology in B_{12} deficiency. However none of the patients with low B_{12} levels had clinical evidence of B_{12} deficiency. Further studies and longitudinal follow up will be necessary to determine whether CIU patients with low B_{12} levels will develop hematological or neurological complications.

References

1. Greaves, M.W. Chronic urticaria. NEJM 1995, 332:1767-1772
2. Sabroe, R.A., Fiebiger, E., Francis, D.M., Maurer, D., Seed, P.T., Stat, C., Grattan, C.E., Black, A.K., Stingl, G., Greaves, M.W., Barr, R.M. Classification of anti-FceRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. J Allergy Clin Immunol 2002, 110:492-429.
3. Ferrer, M., Kinet, J.P., Kaplan A.P. Comparative studies of functional and binding assays for IgG anti-FceRIa (a-subunit) in chronic urticaria. J Allergy Clin Immunol 1998, 101: 672-676.
4. Fiebiger, E., Hammerschmid, F., Stingl, G., Maurer, D. Anti-FceRIa autoantibodies in autoimmune mediated disorders. J Clin Invest 1998, 101:243-251.
5. Kikuchi, Y., Kaplan, A.P. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. J Allergy Clin Immunology 2002, 109:114-118.
6. Heymann, W.R. Chronic urticaria and angioedema associated with thyroid autoimmunity: Review and therapeutic implications. J Am Acad Dermatol 1999, 40:229-232.
7. Lee, G.R. Megaloblastic and nonmegaloblastic macrocytic anemias. In: G.R. Lee, T.C. Bithell, J. Foerster, J.W. Athens, J.N. Lukens (Ed.) Wintrobe's Clinical Hematology. Philadelphia: 1993, pp. 745-807.
8. Wedi, B., Wagner, S., Werfel T., Manns, M.P., Kapp, A. Prevalence of Helicobacter pylori-associated gastritis in chronic urticaria. Int Arch Allergy Immunol 1998, 116:288-294.
9. 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, 39:443-445.
10. Negrini, R., Savio, A., Poiesi, C., Appelmelk, B.J., Buffoli, F., Paterlini, A., Cesari, P., Graffeo, M., Vaira, D., Franzin G. Antigenic mimicry between Helicobacter pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. Gastroenterology 1996, 111(3):655-665.
11. Carmel, R., Perez-Perez G.I., Blazer, M.J. Helicobacter pylori infection and food-cobalamin malabsorbtion. Dig Dis Sci 1994, 39:309-314.
12. Appelmelk, B.J., Simoons-Smit, I., Negrini, R., Moran, A.P., Aspinall, G.O., Forte, J.G., De Vries, T., Quan, H., Verboom, T., Maaskant, J.J., Ghiara, P., Kuipers, E.J., Bloemena, E., Tadema, T.E., Townsend, R.R., Tyagarajan K., Crothers, J.M., Monteiro, M.A., Savio, A., De Graaf, J. Potential role of molecular mimicry between Helicobacter pylori lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect Immunol 1996, 64:2031-2040.
13. Kaptan, K., Beyan, C., Ural, U.A., Cetin, T., Avcu, F., Gulsen, M., Finci, R, Yalcin A. Helicobacter pylori-Is it a novel causative agent in vitamin B12 deficiency? Arch Intern Med 2000, 160:1349-1353.
14. Appelmelk, B.J., Faller, G., Claeys, D., Kirschner, T., Vandenbroucke-Grauls C.M. Bugs on trial: the case of Helicobacter pylori and autoimmunity. Immunol Today 1998, 19(7):296-299.
15. Carmel, R. Cobalamin, the stomach and aging. Am J Clin Nutr 1997, 66:750-759.
16. Carmel, R., Aurangzeb. I., Qian, D. Associations of food-cobalamin malabsorption with ethnic origin, age, Helicobacter pylori infection, and serum markers of gastritis. Am J Gastroenterol 2001: 96(1);63-70.
17. Antony, A.C. Megaloblastic anemias. In R. Hoffman, E.J. Benz, S.J. Shattil, B. Furie, H.J. Cohen (Ed.), Hematology, Basic Principles and Practice. New York: Churchill Livingstone Press 1991, 392-422.
18. Simon, J.A., Hudes, E.S. Relation of serum ascorbic acid to serum vitamin B12, serum ferritin, and kidney stones in US adults. Arch Intern Med 1999, 159 (6): 619-624.
19. Babior, B.M., Bunn, H.F. Megaloblastic anemias. In: E. Braunwald, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J.L. Jameson (Ed.) New York: 2001, 674-680.
20. Stabler, S.P., Allen, R.H., Savage, D.G., Lindenbaum, J. Clinical Spectrum and Diagnosis of Cobalamin Deficiency. Blood 1990, 76(5):871-881.
21. Altus, P., Blandon, R., Wallach, P.M., Flannery, M.T. Case report: the spectrum of autoimmune thyroid disease with urticaria. Am J Med Sci 1993, 306:379-380.
22. Armstrong, J.L. II, Stafford, C.T. Chronic idiopathic(?) urticaria: a satisfactory outcome. Ann Allergy Asthma Immunol 1999, 83:93-98.

23. Naimeh, L.G., Muller, B.A. Chronic urticaria in a 17-year-old patient with a past history of bowel disease. Ann Allergy Asthma Immunol 2001, 86:511-516.
24. Campli, C., Gasbarrini, A., Nucera, E., Franceschi, F., Ojetti, V. Beneficial effects of Helicobacter pylori eradication on idiopathic chronic urticaria. Dig Dis Sci 1998, 43(6):1226-1229.
25. Schiotani, A., Okada, K., Yanaoka, K., Hidekozu, I., Nishioka, S., Sakurane, M., Matsunaka, M. Beneficial effects of Helicobacter pylori eradication in dermatologic diseases. Helicobacter 2001, 6(1):60-65.

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