DOI: 10.4149/BLL_2012_109

BRATISLAVA MEDICAL JOURNAL
BRATISLAVSKÉ LEKÁRSKE LISTY

Bratisl Lek Listy 2012; 113 (8)
495–497

CLINICAL STUDY

Celiac disease and multiple sclerosis in the northwest of Iran

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Abstract: *Objective:* To compare the frequency of celiac disease (CD) in patients with multiple sclerosis (MS) and healthy controls using tissue transglutaminase IgA antibodies (anti-tTGA) as a screening tool.
Background: CD and MS are immune-mediated diseases, and it has been hypothesized that the genetic similarities between these conditions can predispose individuals to suffer from both. Data regarding this association are limited, particularly in Eastern countries.
Methods: One hundred clinically defined MS patients were randomly selected from Tabriz, northwest of Iran. The control group consisted of 121 age- and gender-matched healthy individuals. All subjects were screened with anti-tTGA. Total IgA was obtained for investigation of IgA deficiency.
Results: The mean age of MS patients (32 male and 68 female) was 33.06±8.79 years; the mean age of controls was 32.98±9.62 years. The mean expanded disability scale score (EDSS) for MS patients was 3.86±1.91. Approximately 78.5 % of MS patients suffered from a remitting relapsing type of MS. All subjects (MS patients and controls) were negative for anti-tTGA. IgA deficiency was demonstrated in 14 % of MS patients and 11 % of controls (p>0.1). No IgA-deficient subjects consented to undergo a duodenal mucosa biopsy.
Conclusion: The present study failed to demonstrate a positive relationship between MS and CD. Therefore, we conclude that there is no basis for recommending the routine screening of MS sufferers for celiac disease *(Ref. 23)*. Full Text in PDF *www.elis.sk*.
Key words: celiac disease, multiple sclerosis, anti-tissue transglutaminase antibodies.

Celiac disease (CD) is an autoimmune enteropathy induced by gluten proteins present in wheat, barley and rye, and characterized by small intestinal lesions of variable severity (1). In its classic form, CD appears with symptoms and signs of intestinal malabsorption. However, there is also a latent form of the disease (2]) The duodenal mucosa of CD patients can be normal or they can present with changes in the mucosa ranging from mild alterations to severe atrophy in mucosal architecture (3). Treatment with a gluten-free diet results in mucosal recovery but recurrence of clinical disease ensues if gluten is returned to the diet (2).

MS is the most common inflammatory-demyelinating disease of the central nervous system (CNS) and the most frequent cause of nontraumatic neurological disability in young and middle-aged adults (4). MS is estimated to affect 400,000 persons in the United States and 2 million people worldwide (5). Women between 20 and 40 years of age are affected twice as frequently as men, and north European Caucasian individuals are especially vulnerable. CD and MS are immune-mediated diseases that are influenced by genetic factors, especially HLA antigen (6, 7). This genetic similarity could result in individuals being at risk of developing both diseases.

Previous research has been focused on the increased levels of anti-gliadin and gluten antibodies in MS patients (8–10). As far as we are aware there have been only two studies assessing the association between CD and MS by using the serological tests (11, 12). There was no evidence of an increased risk of CD in MS patients in either study. In a recent case report, gluten sensitivity was reported in two cases of neuromyelitis optica (13).

This study has been carried out as there have been few investigations into the association between CD and MS, particularly in Eastern countries. Should the latter association be confirmed, the screening of MS patients for CD could be of use in view of the probable efficacy of a gluten-free diet in improving the symptoms of MS. The aim of the present study was to investigate the prevalence of CD among patients with MS in northwest Iran.

Methods

One hundred patients with MS who had been diagnosed on the basis of McDonald criteria (14) were randomly recruited from outpatient clinics of Tabriz. The control group consisted of 121 age- and gender-matched healthy blood donors with no history of autoimmune diseases or CD. Patients in the aggressive phase of the disease and/or undergoing treatment with glucocorticoids

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or immunosuppressive drugs were excluded from the study. All MS patients were interviewed and assessed by a physician with regard to the onset of MS symptoms, type of MS, and disability score based on expanded disability scale score (EDSS). The study was approved by the Ethics Committee of the Tabriz University of Medical Sciences.

Fasting blood (5 ml) was collected from patients and control subjects. Samples were centrifuged; serum was extracted and divided into two aliquots, and immediately stored at –20 °C. Levels of anti-tissue transglutaminase IgA antibodies (anti-tTGA) were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) using human recombinant anti-tTGA as the antigen (Eu-tTG IgA, Eurospital, Trieste, Italy). A value of anti-tTGA over 7 AU/ml was considered positive. Having in mind that (a) anti-tTGA is not appropriate for patients with IgA deficiency, and that (b) 2–3 % of the celiac disease population suffer from IgA deficiency (13), false-negative results were eliminated by determining the serum IgA levels before measuring the anti-tTGA levels. The total serum IgA levels were determined by turbidimetry, and a level below 70 ng/dl was considered IgA deficient.

Data are presented as mean ± standard deviation or as percentages where appropriate. Statistical analysis was performed using the Statistical Package for Social Science (SPSS) for Windows version 11.5 using Chi-square and t-tests for comparison. A p value of less than 0.05 was considered statistically significant.

Results

In the present research, 100 patients with MS were studied. The mean durations since the diagnosis of MS and the onset of symptoms were 3.6±3.3 years and 5.7±5.5 years, respectively. The mean EDSS was 3.86±1.91. Approximately 78.5 % of subjects suffered from remitting relapsing MS and 13.9 % had secondary progressive MS. Ninety-one percent of the MS patients reported a history of using several interferon preparations such as Avonex (46.9 %), Rebif (18.5 %) and Betaferon (34.6 %).

Serological screening for CD based on tTG was performed in 100 study subjects (32 male and 68 female) aged 33.1±8.8 years (range, 12–57 years) and in 121 healthy control subjects (46 male and 75 female) aged 32.98±9.62 years (range, 16–50 years; $p>0.1$). Anti-tTGA screening results were negative for all subjects (patients and control group). However, 14 % of MS patients and 11.5 % of the control group were IgA deficient ($p>0.1$). None of the IgA deficient subjects consented to undergo a duodenal mucosa biopsy.

Discussion

In the present study, the results of anti-tTGA screening were negative in both MS patients and controls. This finding is in agreement with previous studies investigating the association between MS and CD. Pengiran Tengah et al demonstrated positive results in 2 % of 49 MS patients using endomysial autoantibodies and in 12 % using an anti-gliadin antibody test (12). However, these results were not statistically significant. Salvatore et al. demonstrated that 95 adult patients with MS did not have pathological values for anti-tTGA test (11). In Sweden, 14,371 patients with CD were compared with 70,096 persons without CD, and no increased risk of MS in patients with CD was evident (15).

The evidence supporting a positive association between CD and MS has been based on genetic and environmental factors. For example, the low plasma level of vitamin D that manifests in CD patients can lead to MS (16–18), and HLA (DR3-DQ2) haplotypes that predispose persons to CD may lead to a modestly increased risk of MS (6). However, the lack of a positive association between MS and CD indicates that these diseases could have a different genetic and immunological basis. An association between type 1 diabetes and MS is under investigation. Some research suggests that the allele DQB1*0602 is associated with a low risk of type 1 diabetes but an increased risk of MS (19, 20). Therefore, based upon the results of these investigations, it could be proposed that alleles that have a role in the predisposition to and pathogenesis of MS could protect against CD or vice versa.

Most recent research concerning the association between CD and MS has been related to the plasma levels of anti-gliadin and gluten antibodies rather than the direct relationship between the two conditions. Circulating antibodies to gliadin and gluten have been considered a sign of CD but could be due to increased permeability. Increased permeability and inflammatory bowel disease among patients with MS have been reported in some studies (21, 22). This increased intestinal permeability leads to increased absorption of gluten and gliadin resulting in the production of IgA antibodies. Anti-gliadin and gluten antibodies are able to cross the blood-brain barrier and aggravate the neural symptoms of MS, explaining the efficacy of a gluten-free diet in alleviating the symptoms of MS.

Most recent studies were cross-sectional and they demonstrated no association between CD and MS. Prospective longitudinal studies with large sample sizes would be preferable for investigating the direct association between these diseases. This study, just as previous cross-sectional ones, failed to demonstrate a positive relationship between MS and CD. However, this research is one of only a few studies performed in Eastern countries concerning this relationship. One of the limitations of the present study was that no IgA deficient subjects consented to undergo a duodenal mucosa biopsy. The anti-tTGA test is one of the most sensitive and specific serological tests for sub-clinical CD diagnosis (23). However, this test cannot be used to screen IgA-deficient patients. Therefore, if IgA-deficient subjects had undergone a duodenal mucosa biopsy, some cases of CD could have been revealed. On the basis of these findings we can demonstrate no grounds for recommending the routine screening of persons with MS for celiac disease. However, prospective longitudinal studies to assess the direct association between MS and CD should be carried out. In addition, it will be valuable to conduct research to examine the genetic differences and similarities between CD and MS, as well as immunological factors that affect them.

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Received March 6, 2010.
Accepted April 15, 2012.