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Multiple sclerosis and gluten sensitivity☆

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Abstract

Objective: To compare the frequency of gluten sensitivity in patients with multiple sclerosis (MS) and healthy controls.
Patients and Methods: The patients were 161 clinically definite MS patients who referred to neurology outpatient clinic of Nemazee Hospital, Shiraz, south of Iran from March 2004 to October 2005. IgG and IgA antigliadin antibodies were measured by enzyme immuno assay (EIA) method. The test of IgA antitranstissue glutaminase (tTG) and duodenal biopsy were carried out in patients with either IgA or IgG AGA positive sera. Antigliadin antibodies were also measured for 166 age and sex matched control group.
Results: Neither IgG nor IgA antigliadin antibodies showed significant differences between MS patients and controls. Anti-tTG antibody and histopathologic studies were negative in all patients with positive IgG or IgA antigliadin antibodies results. Mean values of IgG and IgA antigliadin antibodies in MS patients with different sex, age, course, and functional systems involvement were not significantly different.
Conclusion: Gluten sensitivity is not associated with MS in Iran.

Keywords: Multiple sclerosis; Gluten; Celiac disease

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system whose pathogenesis is still unclear. MS is sometimes difficult to be differentiated from CNS involvement in systemic autoimmune diseases [1].

Celiac disease (CD) is an inflammatory autoimmune disease of the small intestine that occurs in genetically susceptible individuals having HLA DQ2 or DQ8 upon exposure to dietary gluten. The disease has extraintestinal manifestations such as dermatological and neurological ones. Some neurological presentations like cerebellar ataxia, myoclonus, dementia, epilepsy, myelopathy, polyneuropathy, mononeuritis multiplex, and myopathy have a reported association with established celiac sprue [2–7]. The neurological dysfunction can not only precede CD, but can also be the only manifestation of gluten sensitivity [8,9]. Neurological presentations can develop in patients with normal nutritional profiles, and may not respond to vitamin supplementation [10]. It is speculated that the neurological involvement may be immunologically mediated, a hypothesis supported by the association with anti-purkinje cell antibodies in patients with cerebellar ataxia and gluten sensitivity [11].

As some neurological manifestations of gluten sensitivity resemble those of MS and gluten sensitivity is relatively prevalent in Iran (1:104) [12], we decided to investigate the prevalence of gluten sensitivity in Iranian MS patients. This

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was conducted by screening with antigliadin antibodies, and then pathological confirmation.

2. Methods and materials

The subjects were 161 clinically definite MS patients (fulfilling Poser's criteria) [13] who referred to neurology outpatient clinic of Nemazee Hospital, Shiraz, south of Iran from March 2004 to October 2005. All patients filled out informed consent. They were asked on age, sex, age of the onset, and duration of MS, symptoms of MS and gastrointestinal (GI) manifestations of CD. A thorough neurological examination was then carried out for all patients. Neurological manifestations were classified into seven functional systems including pyramidal, cerebellar, brainstem, sensory, sphincteric, visual, and cerebral presentations.

Five cc clot blood was taken from all patients. IgG and IgA antigliadin antibodies (AGA) were measured by enzyme immuno assay (EIA) method (Binding Site, Bindazyme human antigliadin EIA Combi kit Birmingham, UK). IgG antigliadin antibody titer of $\geq$10 unit/ml and IgA antigliadin antibody $\geq$5 unit/ml was considered positive.

The IgA anti-transtissue glutaminase (tTG) was tested in either IgA or IgG AGA positive patients by EIA method (Binding site, Bindazyme human tTG EIA kit, Birmingham, UK). The titer $\geq$4 unit/ml was considered positive. Upper GI endoscopy with visualization of the second portion of the duodenum was performed for all AGA positive patients and biopsy from this region was taken.

One hundred and sixty six age and sex matched healthy persons who referred to Iran blood transfusion organization for blood donation were recruited as control group. IgA and IgG AGA were measured for them.

The statistical analysis of the findings was performed using Mann–Whitney U test and Spearman coefficient correlation test. P value $\leq$0.05 was considered significant. SPSS program version 13.0 was used for computerized analysis.

3. Results

One hundred and twenty one (75.1%) patients were female and 40 (24.9%) were male. The mean and standard deviation of the age of the patients were 31.9 ± 9.6 years. Among the patients, 110 (68.3%) were from urban areas and 51 (31.6%) patients were from rural areas.

The most common MS course was relapsing-remitting (RR) which accounted for 112 (69.5%) patients. Secondary progressive (SP) course accounted for 28 (17.3%) patients, and 18 (11.1%), 2 (1.2%) patients had primary progressive (PP), and relapsing progressive (RP) course, respectively.

Sensory system was the most common functional system, which was involved in 83.6% of patients. Cerebellar, pyramidal, visual, brain stem, sphincteral, and cerebral systems were involved in 74.3, 65.6, 57.9, 42.1, 33.9, and 9.2% of the patients, respectively. Three (1.8%) patients had a history of abdominal distention, 2 (1.2%) had history of diarrhea, and 1 (0.6%) had history of weight loss. None of the patients had history of steatorrhea. Positive family history of CD was absent among patients.

Six (3.7%) patients had positive IgG AGA and 5 (3.1%) positive IgA AGA. No one was positive for both. Mean value and standard deviation of AGA titer were 3.62 ± 2.75 for IgG type and 2.13 ± 1.29 for IgA type. 95% confidence intervals were 3.62 ± 0.42 and 2.13 ± 0.199 for IgG and IgA AGA, respectively. Among healthy controls, 5 (3%) and 6 (3.6%) were positive for IgG and IgA AGA, respectively. The mean value and standard deviation of AGA titer in the controls were 4.02 ± 2.38 for IgG type and 2.09 ± 1.52 for IgA type. Ninety-five percent confidence intervals were 4.02 ± 0.36 and 2.09 ± 0.23 for IgG and IgA AGA, respectively.

Anti-tTG antibody was negative in all patients with positive IgG or IgA AGA results. For all 11 patients who were positive for either IgG or IGA AGA, upper gastrointestinal endoscopy, and duodenal biopsy were carried out. No one had any pathologic evidence in favor of CD.

Comparison of the mean values of IgG and IgA AGA showed no significant difference between patients and controls ($p = 0.11$ and 0.26 for IgG and IgA AGA, respectively). Values of AGA were not significantly different between male and female MS patients ($p = 0.06$ and 0.598 for IgG and IgA AGA, respectively). Age distribution and AGA levels were also not correlelated ($p = 0.86$ and 0.96 for IgG and IgA, respectively). Comparison of mean values of IgG and IgA AGA in different MS courses demonstrated no significant differences ($p = 0.95$ and 0.37, 0.54 and 0.68, 0.79 and 0.51 for RR, primary progressive, and SP, respectively). Comparison of mean values of AGA in patients with different MS functional system involvement also showed no significant differences: sensory ($p = 0.25$ and 0.92 for IgG and IgA AGA, respectively), cerebellar ($p = 0.65$ and 0.37), brain stem ($p = 0.83$ and 0.42), pyramidal ($p = 0.22$ and 0.79), sphincteral ($p = 0.79$ and 0.46), visual ($p = 0.19$ and 0.78), and cerebral ($p = 0.82$ and 0.47).

4. Discussion

Association of gluten sensitivity and neurological disorder is a very controversial issue. Some researchers recommended IgG AGA as part of the routine batteries for all patients with neurological dysfunction of obscure etiology [9]. In the other hand, other investigators decisively criticized this approach [14].

Overall, our study showed that neither IgG nor IgA antigliadin antibodies showed significant difference between MS patients and controls. Anti-tTG antibody and histopathologic studies were also negative in all patients with positive

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IgG or IgA antigliadin antibodies results. Sex, age, course, and functional systems involvement were not significantly different between MS patients with and without antigliadin antibodies.

There are a few researches, which have investigated the association of MS and gluten sensitivity. All of them were carried out in western countries.

In Tengah's et al. study, IgG and IgA AGA were found in 6 out of 49 (12%) and 3 out of 49 (6%) MS patients, respectively. These ratios were similar to those of control group. IgA tTG was found in 3 out of 49 patients, again similar to controls. They identified two patients with MS-like disease who were incidentally discovered to have occult CD. In these patients, occult CD was suspected following the serologic clues (antigliadin antibodies IgG and IgA). However, Tengah et al. mentioned that they couldn't exclude the possibility that these two patients have developed an inflammatory disease of the CNS associated (directly or indirectly) with gluten sensitivity [15].

Hadjivassiliou et al. screened 100 patients with RR or SP MS, and found the prevalence of antigliadin antibody to be 10%, the same as healthy population. Also they investigated five patients who had gluten sensitive enteropathy and MS-like symptoms. All of those had cerebellar dysfunction, and two had peripheral neuropathy. They proposed that gluten sensitivity should be considered as the etiology of atypical primary progressive MS particularly where ataxia is the prominent feature [16]. In spite of their speculation, AGA antibodies were not significantly higher in our patients with primary progressive course or cerebellar dysfunction in comparison to other types of MS.

Our results are also consistent with two previous studies, which demonstrated that intestinal biopsies in patients with MS showed no histopathologic evidence of CD [17,18].

The shortcomings of this current study were lack of measurement of anti-endomysial antibody (EMA), HLA typing for HLA DQ2 and staining for interaepithelial T cell subpopulations in AGA positive patients.

To the best of our knowledge, this is the study with the largest sample size, which demonstrates the loss of significant association between MS and gluten sensitivity in a nonwestern population. The major advantage of our study was the exclusion of gluten sensitivity by pathological confirmation of immunologically screened patients. Our results instill doubts into one's mind about the value of routine investigation of AGA or prescription of gluten free diet for MS patients.

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