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Short report

Multiple sclerosis and celiac disease: is there an increased risk?

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Multiple sclerosis and celiac disease are both considered immune-mediated diseases. Recently, improved serological screening methods provided a higher prevalence of celiac disease (CD) in the general population worldwide and also demonstrated gastrointestinal symptoms may be lacking. The aim of this study was to determine the prevalence of (CD) in an unselected group of 95 adults with multiple sclerosis using transglutaminase antibodies. No patients showed pathological values. Different immune and genetic basis between the two diseases may represent crucial insights to explain our results.

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Key words: multiple sclerosis; celiac disease; transglutaminase; interferon; gastrointestinal disease

Introduction

Celiac disease (CD) is a common gluten-mediated autoimmune enteropathy with multiple extraintestinal involvements.¹ Different neurological manifestations have been reported in celiac patients although the pathogenic mechanisms are still unclear.² Multiple sclerosis (MS) is a complex chronic neurological disease with suspected autoimmune pathogenesis.³ Concomitant autoimmune diseases are reported in MS but the association of MS with CD has not been widely explored. The aim of this study was to establish the prevalence of CD by transglutaminase antibodies in a group of patients with MS.

Patients and methods

We recruited 95 consecutive adult patients (mean age 41.3 years, range 21–63 years) with MS (76 relapsing–remitting, three primary–progressive and 16 secondary–progressive MS) attending the MS outpatient follow-up clinic. Forty-six patients were on recombinant interferon (IFN)- β -1a treatment. IgA-tissue transglutaminase antibodies (tTG) were measured by an ELISA method (EutTG, Eurospital, Trieste, Italy).

100 μ L serum (diluted 1:26) was pipetted into wells with coated human tTG. After incubation for 60 min, 100 μ L horseradish peroxidase-labelled sheep anti-human

IgA was pipetted into each well and, after a second incubation for 60 min, 100 μ L of the chromogenic substrate (tetramethylbenzidine) was added. After a further incubation for 30 min, 100 μ L H₂SO₄ was added into each well to cease the reaction. The optical density (OD) value was read at 450 nm. The anti-tTG value was expressed in arbitrary units (AU), calculated as follows:

OD sample (450 nm) / 3 AU calibrator

(positive control serum) / OD calibrator (450 nm)

Normal levels of tTG were considered below 7 AU/ml in accordance with manufacturers' instructions. Total serum IgA values were also determined in all subjects using an immunoturbidometric assay (Roche Diagnostics, Milan, Italy) and serum levels below 0.05 g/L were considered indicative of selective IgA deficiency.

We considered the prevalence (1:174) recently reported by Volta *et al.*⁴ in a survey of unselected normal adult population living in North Italy as control data for prevalence of CD. The Mann–Whitney test was employed for statistical analysis. All patients signed informed consent and the Ethical Committee of our hospital approved the study.

Results

All patients presented normal values of tTG and total serum IgA. Levels of tTG did not show any significant correlation with MS course, disease duration or severity. Overall, the mean level of disability in our patients was 2.5 and was 6.2, 3.4 and 2.2 in primary progressive, secondary–progressive and relapsing–remitting patients, respectively. Patients treated with IFN- β -1a presented upper levels of mean tTG compared to non IFN-treated

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Table 1 Correlation between values of transglutaminase, treatment and clinical phase of MS

Clinical course of MS	Patients (n)	Mean values of tTG (AU)
Total MS patients	95	0.9
IFN-treated	46	1.1
IFN-untreated	49	0.8
Relapsing-remitting	76	0.9
IFN-treated	37	1.0
IFN-untreated	39	0.8
Primary-progressive	3	1.1
IFN-treated	1	0.7
IFN-untreated	2	1.3
Secondary-progressive	16	1.1
IFN-treated	8	1.3
IFN-untreated	8	0.8

MS = multiple sclerosis; tTG = transglutaminase; AU = arbitrary unit; IFN = interferon- β -1a.

patients (1.1 versus 0.8 AU/ml) but without any meaningful significance ($P = \text{NS}$). Data of patients are shown in Table 1. No patients reported gastrointestinal symptoms or known gastrointestinal disease.

Discussion

Immune dysregulation and impaired apoptosis are shared findings in CD and MS supporting the hypothesis of an increased association between the two diseases. Furthermore, neurological involvement has been reported in CD^{2,5} with disappearance of symptoms for a gluten free diet (GFD) in a proportion of early treated patients.⁵ Increased prevalence of autoimmune manifestations has also been demonstrated in untreated CD¹ and in treated MS.^{6,7} Our patients treated with IFN- β only presented a mild higher level of tTG but within the normal range and without significance.

Up to now the relationship between CD and MS has never been widely investigated. A GFD with additional minerals and vitamins caused some clinical improvement in a small group of MS patients without a proven CD diagnosis.⁸ In two other small studies duodenal biopsies were pathological in 3/26 total MS patients. No patients presented gastrointestinal symptoms.^{9,10} In 147 patients with different neurological manifestations² positive anti-gliadin antibodies (AGA) were observed in 57% of patients but in only 35% the diagnosis of CD was confirmed. Only 1/12 patients with MS presented positive AGA but refused the biopsy.² The term 'gluten sensitivity' was thus introduced to describe the presence of positive antigliadin levels without intestinal involvement. The low specificity of AGA for CD in neurological patients was subsequently confirmed by other studies.^{11,12} The relationship between 'gluten sensitivity' and CD still needs to be clarified.¹² Tissue transglutaminase has been recently identified as specific auto-antigen of CD¹³ and nowadays represents the most reliable diagnostic test for CD. Our study is the first one testing CD in MS using tTG but we did not find any

positive MS patient in our population. In North Italy the prevalence of CD has been recently estimated to be about 1:174 normal adults.⁴ Hence, although our sample was small, this is the biggest study investigating CD in MS so far. The absence of gastrointestinal symptoms in our group cannot be considered critical for the lack of diagnosis of CD as showed in previous reports.^{2,14,15}

Different cytokine expression and HLA pattern (HLA-DQ2 (*DQA1*05/DQB1*02*) or HLA-DQ8 (*DQA1*03/DQB1*0302*) genes in CD¹⁶ versus DRB1*1501-DQB1*0602 or DR2 in MS¹⁷) are more likely decisive in excluding an increased CD prevalence in MS.

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