Association of celiac disease in patients with multiple sclerosis in Tuscany

Barbara Piccini[1], Monica Ulivelli[2], Maria Pia Amato[3], Sabina Bartalini[4], Mario Falcini[5], Marta Giannini[6], Eliana Magnani[7], Luca Massacesi[8], Anna Maria Repice[7], Marina Vascotto[9] and Salvatore Grosso[10]

[1]Tuscany Regional Centre of Pediatric Diabetes. Pediatric Department. Meyer Children's Hospital. Florence, Italy. [2]Neurology and Neurophysiopathology Department. Center for Multiple Sclerosis. University of Siena. Siena, Italy. [3]Department of NEUROFARBA. Section Neurosciences. University of Florence, Florence. Italy. Institute Don Gnocchi. Florence, Italy. [4]Neurology and Neurophysiopathology Department. Center for Multiple Sclerosis. University Hospital Santa Maria alle Scotte. Siena, Italy. [5]Neurology Department. Santo Stefano Hospital. Prato, Italy. [6]Department of NEUROFARBA. Section Neurosciences. University of Florence. Florence, Italy. [7]Division Neurology 2. Careggi University Hospital. University of Florence. Florence, Italy. [8]Department of Neurosciences. Careggi University Hospital. University of Florence. Florence, Italy. [9]Clinical Pediatrics. Department of Pediatrics. University Hospital Santa Maria alle Scotte. Siena, Italy. [10]Clinical Pediatrics. Department of Pediatrics. University of Siena. Siena, Italy

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Correspondence: Barbara Piccini. Tuscany Regional Centre of Pediatric Diabetes. Pediatric Department. "A. Meyer" University Children's Hospital. Viale Pieraccini, 24 I-50139 Florence, Italy. **e-mail:** b.piccini@meyer.it

ABSTRACT

Background and study purpose: to describe the comorbidity of celiac disease among a large cohort of multiple sclerosis patients in Tuscany.

Methods: the association of celiac disease among multiple sclerosis adult patients (n=2050) was retrospectively evaluated.

Results: 13 patients were diagnosed with celiac disease, the female:male ratio was 3.3:1 and the median age at diagnosis was 34.2 years (SD 13). Seventy-seven per cent of subjects complained about gastrointestinal symptoms. IgA anti- transglutaminase was positive in 85 % of cases and there was 70 % of villous atrophy.

Conclusions: the frequency of celiac disease among multiple sclerosis patients examined was lower than in the general population (0.6 % *vs* 1 %) (p = 0.65).

Keywords: Celiac disease. Multiple sclerosis. Epidemiology. Comorbidity.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). Multiple sclerosis-like diseases and a headache associated with brain white-matter lesions (WMLs), which are documented by magnetic resonance imaging (MRI), have been reported in celiac disease (CD) patients (1). No conclusive data support the hypothesis that there is an increased prevalence of MS in patients with CD and of CD in patients with MS. The possible relationship between CD and MS was first recorded in 1965, when the pathogenesis of CD was not completely understood (2). MS and CD share common aspects of a dysregulation of the immune system and they are both inflammatory diseases due to T cell-mediated immunity. The aim of this study was to describe the association of CD among a large cohort of MS patients in Tuscany, compared to the prevalence of CD among the general population.

METHODS

The frequency of CD was retrospectively evaluated among a cohort of 2050 adult patients with MS followed-up during 2016 that were included in the database of the Centers for the diagnosis and treatment of MS in Firenze, Prato and Siena. MS cases were diagnosed between 1985 and 2015, based on the McDonald criteria and subsequent revisions (3).

Patients who presented with gastrointestinal or extra-intestinal symptoms evocative of CD and/or with iron or vitamin

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deficiency, underwent serologic tests for CD, including tissue transglutaminase IgA antibodies (tTG-IgA), anti-endomysium IgA antibodies (EMA) and/or antibodies against deaminated gliadin peptides (DGP), together with dosage of total IgA levels. An esophagogastroduodenoscopy (EGDS) with small intestine biopsies was performed in subjects with a positive serology, in order to confirm CD diagnosis. The diagnosis was made according to the revised criteria of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) modified in 1990 (4) and after 2012, according to the new ESPGHAN guidelines (5). A CD prevalence of 1:100 was considered in the general population, based on regional differences in Europe where the prevalence varies from 0.3 % in Germany to 2.4 % in Finland (6). Statistical significance was calculated using 2 x 2 contingency tables and the χ^2 test and corrected with the Fisher exact test when sample sizes were small. Values of $p < 0.05$ were considered as significant.

RESULTS

CD was diagnosed in 13/2050 patients attending 4 MS centers in 3 hospitals in Tuscany region, including 3 males with a median age at CD diagnosis 34.2 years (SD 13) (Table 1). The median age at MS diagnosis was 28.8 years (SD 10.8) and 77 % of patients were female (F:M 3.3:1). Most patients were self-sufficient and in the classification of MS subtypes, the relapsing-remitting form was the most common (61 % of cases). Thirty-one per cent of patients were first diagnosed with CD and they started a gluten free diet (GFD) before being diagnosed with MS, 54 % of patients were diagnosed with CD after MS and 15 % of patients were diagnosed with CD and MS simultaneously. Seventy-seven per cent of the subjects complained about gastrointestinal symptoms. tTG-IgA levels were measured in all patients and tested positive in 85 % of cases. Patient 11 was negative for tTG IgA, EMA and DGP and was treated ab initio with monoclonal antibodies. The negative tests results were in contrast to the presence of histologically documented atrophic lesions (Marsh-Oberhuber 3C) (7) and with gastrointestinal symptoms consistent with CD, even though HLA-DQ2/DQ8 were negative. Patient 13 complained about abdominal pain that disappeared after gluten elimination, despite negative CD antibodies. This factor, a positive family history of CD and the presence of HLA-DQ2 homozygosity suggested a potential CD. Duodenal biopsies were performed in 12/13 patients (one patient refused). 70 % of subjects had a histological pattern indicative of CD with villous atrophy (Marsh-Oberhuber 3 A, B or C). Patient 10 had mild histological lesions (Marsh 1), positive IgA-tTG and DGP antibodies, gastrointestinal symptoms and positive DQ2, indicating a potential CD. Patient 4 presented with a normal duodenal histology but moderate chronic gastritis,

Table 1. *Clinical data, serology, histology and haplotype among 13 patients with MS/CD*

	Sex	Age at CD diagnosis	Histology*	Serology	Genetics DQ2/DQ8	GI symptoms	Extra-GI symptoms	Associated diseases
P1	m	29	3A	tTG +	Not performed	Pyrosis	Anemia	No
P2	m	51	3B	tTG +	Not performed	Diarrhea - bloating	Asthenia	No
P3	f	30	Not performed	tTG + EMA +	DQ2	Diarrhea-stypsis	No	No
P4	f	46	Normal (duodenal, chronic gastritis)	tTG + EMA+	DQ2	Diarrhea	No	No
P5	f	2	3C	tTG +	Not performed	No	No	T1DM
P6	f	30	3C	tTG +	Not performed	No	No	T1DM
P7	f	40	3C	tTG +	Not performed	No	Asthenia-anemia	No
P8	f	30	3C	tTG + EMA+	Not performed	Stypsis dyspepsia	No	Depression
P9	m	46	3C	tTG +	DQ2	Pyrosis bloating	Anemia	No
P10	f	43	1	tTG + DGP+	DQ2	Acholic feces	Anemia	No
P 11	f	38	3C	tTG- DGP- EMA -	DQ2/DQ8 negative	Abdominal pain	No	No
P12	f	40	3C	tTG +	Not performed	Abdominal pain, diarrhea, weight loss	No	No
P13	f	20	Normal	tTG - EMA -	DQ 2	Dyspepsia abdominal pain	No	No

*Modified Marsh-Oberhuber classification (7).
m: male; f: female; tTG: antibodies anti transglutaminase; EMA: antibodies anti- endomysial; DGP antibodies anti deamidated gliadin peptide; GI: gastrointestinal; T1DM type 1 diabetes mellitus.

positive IgA-tTG and EMA, a permissive haplotype (DQ2 positive) and gastrointestinal symptoms such as diarrhea. Thus, CD was suspected. Patient 13 had potential CD, as mentioned previously. DQ2 and DQ8 were investigated in 46 % of cases. Predisposing HLA-DQ2 and HLA-DQ8 were negative in just one patient (patient 11). All patients with permissive haplotype showed DQ2.

Only patient 11 repeated EGDS after 10 months of GFD and the atrophic lesions had reverted from Marsh-Oberhuber type 3C to type 1. This patient presented with negative serology without a predisposing haplotype and a third endoscopy was not performed. In conclusion, a CD diagnosis was made in 13/2050 patients with MS, with a prevalence of 0.6 % in the cohort of patients considered. There were no differences between CD prevalence among MS patients and the general population (p 0.65).

DISCUSSION

The present study does not support an increased frequency of CD among MS patients. Moreover, the data surrounding clinical presentation of CD among MS patients mainly indicate an atypical presentation with non-specific gastrointestinal symptoms and extraintestinal manifestations. In this study, gastrointestinal symptoms were present in 77 % of patients and 38 % of subjects had diarrhea as the main symptom.

Since 1966, a variety of neurological disorders have been reported in association with CD (8). The mechanisms implicated in the pathogenesis of neurological disorders associated with CD are not completely understood, due to the fact that only some subjects develop CNS symptoms and the extreme variability of these symptoms. TG6 represents a useful marker of the neurological manifestations in CD patients (9). MS and CD are inflammatory T-cell-mediated autoimmune diseases. However, the evidence is insufficient to support an increased frequency of CD among MS patients and conversely of MS among CD patients, despite these shared etiological aspects. Nicoletti et al. (10) evaluated the presence of CD related antibodies in 217 patients with MS and 200 healthy controls and there was only one control with CD specific antibodies. On the other hand, Rodrigo et al. (11) reported an increased prevalence of biopsy-proven CD in 8 out of 72 MS patients (11.1 %). Ludvigsson et al. (12) evaluated the comorbidity of CD-neurodegenerative/neuroinflammatory diseases using data from the Swedish national register. CD was positively associated with polyneuropathy but not with MS. The strength of the present study is the large sample size, the expertise on immunological diseases of highly specialized centers in a third level hospital and the multidisciplinary approach. Some limitations must be highlighted: (i) only patients with evocative symptoms underwent serological screening and it is possible that CD was under-diagnosed due to the fact that cases with paucisymptomatic or silent CD were missed; (ii) HLA-DQ2 or HLA-DQ8 molecules were investigated in only 46 % of CD-MS patients; and (iii) it should be taken into account that the positivity of serological markers for CD in these patients could be influenced by MS therapies.

In conclusion, this study highlights the usefulness to implement a case-finding strategy in order to address the issue of comorbidity CD-MS. HLA-DQ2 and HLA-DQ8 typing would allow the identification of patients with MS who are at risk and should be periodically screened for CD. This is likely due to the strong negative predictive value of DQ2-DQ8 aplotype and the different HLA class II susceptibility to MS (DQB1*0602 or DR2). On the other hand, CD should be retained as a red flag for a particular diagnostic caution in patients with non-specific MS symptoms and/or WMLs.

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