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Serological prevalence of celiac disease in Brazilian population of multiple sclerosis, neuromyelitis optica and myelitis

Pérola de Oliveira [a,*], Daniel Rocha de Carvalho [b], Ivar Viana Brandi [c], Riccardo Pratesi [d]

[a] Medical neurologist, Department of Neurology, Sarah Network of Rehabilitation Hospitals, SMHS Quadra 501 Conj. A, Brasilia, DF 70.330-150 Brazil
[b] Medical geneticist, Department of Genetics, Sarah Network of Rehabilitation Hospitals, Brasilia, Brazil
[c] Medical neurologist, Department of Neurology, Sarah Network of Rehabilitation Hospitals, Salvador, Brazil
[d] Research Center on Chronic and Immunogenetic Diseases of the Faculty of Medicine, University of Brasilia, Brasilia, Brazil

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ABSTRACT

Purpose: Comorbidity of celiac disease with demyelinating diseases of the central nervous system has been reported since the 1960s. The objective of this study was to determine the serological prevalence of celiac disease in the largest series of patients diagnosed with multiple sclerosis, neuromyelitis optica, or myelitis.
Methods: A prevalence study was conducted with patients evaluated at Sarah Network of Rehabilitation Hospitals between March 2012 and September 2013. They were previously diagnosed with multiple sclerosis, neuromyelitis optica, or idiopathic myelitis. The serum levels of antibodies against tissue transglutaminase and endomysium were assessed.
Results: Of the 379 patients evaluated, 249 (65.70%) were diagnosed with multiple sclerosis, 37 (9.56%) with neuromyelitis optica, and 96 (24.54%) with idiopathic myelitis. Two patients (0.53%), one with multiple sclerosis and other with myelitis, tested positive for both antibodies.
Conclusion: Our study do not confirm the relationship between celiac serological antibodies with multiple sclerosis, neuromyelitis optica and inflammatory myelitis of an unknown etiology.

1. Introduction

Autoimmune disorders consist of a wide array of diseases that may affect a single organ, although most of the characterized disorders are multisystemic (Aminoff, 2008).

Some autoimmune disorders specifically affecting the central nervous system (CNS) include multiple sclerosis (MS), neuromyelitis optica or Devic's disease (NMO), and transverse myelitis, and they are demyelinating, inflammatory, and neurodegenerative disorders (Bushara, 2005; Green and Cellier, 2007). They are associated with B- and T-cell activation, production of cytokines and activation of complement system components and immunoglobulins (Ludvigsson and Green, 2011; Molberg et al., 2000).

During diagnostic investigation of demyelinating diseases, it is not unusual to find autoantibodies that target antinuclear factor (ANF), rheumatoid factor (RF) and extractable nuclear antigen antibody (anti-ENA) which suggests the presence of an autoimmune disorder or autoimmune status (Catassi and Fasano, 2010).

Characterized by multisystem involvement, celiac disease (CD) or gluten-sensitive enteropathy is an autoimmune disorder associated with inflammation of the small intestine with progressive villous atrophy and crypts hypertrophy. CD affects approximately 1% of the Western population and it is significantly influenced by genetic factors, with an approximately 10% prevalence in first-degree relatives (Burgin-Wolff et al., 2013; James and Scott, 2001).

Neurological symptoms of CD are rare in children, but are observed in 10–36% of adults. Cerebellar ataxia, dementia, myelopathy, polyneuropathy, progressive leukoencephalopathy, seizures, and the presence of occipital calcifications are well documented in neuroimaging scans. Some patients may have few or no gastrointestinal symptoms at the onset of neurological symptoms of the disease (Aminoff, 2008; Bushara, 2005).

CD diagnosis is made by clinical suspicion and laboratory tests. The presence of tissue transglutaminase antibodies (IgA-tTG) and endomysium antibodies (IgA-EMA) indicates a 95% diagnostic certainty when found above the criterion threshold. Anti-gliadin antibodies are less reliable and more likely to yield a false positive.

* Corresponding author.
E-mail addresses: 12918@sarah.br (P. de Oliveira), danielcarvalho@sarah.br (D.R. de Carvalho), 205364@sarah.br (I.V. Brandi), pratesir@unb.br (R. Pratesi).

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The gold standard diagnostic test for CD is a duodenal biopsy (Green and Cellier, 2007; Catassi and Fasano, 2010). However, it can be normal in part of the cases. The sensitivity of biopsy is approximately 90% (Burgin-Wolff et al., 2013) and it contribute to reduce the application of this invasive procedure.

There is association between CD and other autoimmune diseases such as rheumatoid arthritis, type I diabetes mellitus, thyroiditis and Sjogren's syndrome (James and Scott, 2001). The comorbidity of demyelinating disease of the CNS, particularly MS, with CD has been suggested by several studies (James and Scott, 2001; Shor et al., 2013; Rodrigo et al., 2011; Nicoletti et al., 2008).

The first positive report of anti-gliadin antibodies and IgA-tTG occurring in MS cases in the 1960s, when the consumption of foods containing gluten was associated with a higher incidence of MS (Shor et al., 2013; Kieslich et al., 2001; Reichelt and Jensen, 2004; Hadjivassiliou et al., 2010). The association between autoimmune diseases is widely acknowledged and documented (Jacob et al., 2005). A possible link between demyelinating diseases of the CNS and CD has been suggested in several studies, but this hypothesis has not been widely investigated. So far, the data published in the literature are still controversial (Salvatore et al., 2004; Hernández-Lahoz and Rodrigo, 2013b). The results are inconsistent and it is unclear whether the higher prevalence of CD in patients with demyelinating disease of the CNS compared to general population is an epiphenomenon or whether it corresponds to the symptomatic spectra of the same illness (Shor et al., 2013; Rodrigo et al., 2011; Nicoletti et al., 2008).

The primary goal is determine the prevalence of CD-related antibodies, IgA class transglutaminase tissue (IgA-tTG), and endomysium (IgA-EMA) in patients with a confirmed diagnosis of MS, NMO, and inflammatory myelitis of an unknown etiology. In addition, we report the demographic characteristics and results of neurological evaluation of this population.

2. Materials and methods

This retrospective study was approved by the Institutional Review Board of SARAH Network of Rehabilitation Hospitals, a network of tertiary public hospitals that treat neurologic diseases and disturbances in gait. This transversal, descriptive study was based on the following criteria. Patients of both sexes aged 16 years or older were included. These patients were admitted for regular medical care between March 2012 and August 2013, after they have been diagnosed with MS, NMO, or myelitis of unknown etiology.

The revised McDonald diagnostic criteria were considered for MS (Polman et al., 2011). Patients with clinical NMO were characterized according to the diagnostic criteria established in Wingerchuk et al. (2006). The Transverse Myelitis Consortium Group was used to establish the diagnostic criteria for idiopathic transverse myelitis.

The data were collected by consulting the electronic medical records. Location of origin, age, disease duration, sex, education level, neurological exam alterations, presence of neurogenic bladder and intestine as well as other symptoms were also considered. For disability evaluation in patients diagnosed with MS, the Kurtzke Expanded Disability Status Scale (EDSS) was used.

Serum analysis for IgA-tTG and IgA-EMA was performed by Enzyme-Linked Immunosorbent Assay (ELISA) and a commercial kit for transglutaminase IgA class antibodies detection (Orgentec Diagnostika GmbH, Germany) were used. The serology was done consecutively for all patients diagnosed with MS, NMO or myelitis. Assay results greater than 10 U/ml were considered positive, and results below this reference value were considered negative. We determine the amount of IgA class anti-endomysium antibodies present using an indirect immunofluorescence method (Euroimmun, Germany) in addition to the commercial kit. For patients with positive results for this assay, a /duodenal biopsy was subsequently recommended (Husby et al., 2012).

The chi-square test was used to analyze the association of several characteristics with the type of diagnosis. Whenever the expected frequency was less than 5 in more than 20% of cases, the exact version of the test was implemented.

3. Results

We evaluated 379 patients diagnosed with MS, NMO or myelitis of unknown origin. The younger patient aged 16 years and the older age patient was 76 years. The age distribution showed a higher number of patients in the group older than 45 years. The sample included patients from the five geographical regions of Brazil, with the largest proportion coming from the Central-West region.

In agreement with the literature, approximately 71% of the subjects were women, yielding a female/male ratio of 2.5:1 (Table 1). Most patients were independent in their daily life, able to perform personal care and daily tasks. In accordance with this finding, over 58% of MS patients showed an EDSS score less than or equal to 4.5, which referring to an outpatient's ability to work and walk for at least 300 m without aid or rest.

MS was the most prevalent diagnosis. In the classification of MS subtypes, the relapsing-remitting form was the most common.

Only two patients tested positive for CD.

One was a 28-year-old male patient, diagnosed with myelitis in 2009. He presented with an IgA-tTG titer 10 times higher (106.5 U/ml) than the reference value (until 10 U/ml) and was positive for IgA-EMA. He has complained of gastrointestinal symptoms such as chronic diarrhea. He died because car accident at the beginning of this study and duodenal biopsy was not performed. According to the consensus criterion (2012) of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (Husby et al., 2012), he was considered affected by CD.

The other patient with a positive serology was a 26-year-old diagnosed with relapsing-remitting MS in 2012. Laboratory tests indicated an IgA-tTG titer of 53.6 U/ml and a positive test for IgA-EMA. The patient was referred to the Gastroenterology service and underwent duodenal biopsy that showed duodenitis with intraepithelial lymphocytosis in a disruptive pattern. The mucosa presented high intraepithelial lymphocyte infiltration and villi appeared atrophic and coated with attenuated and vacuolated epithelium. Crypts appeared hyperplastic. These findings confirm the serological CD diagnosis.

Table 1
Demographic characteristics.

Characteristics	Multiple Sclerosis	NMO	Idiopathic Myelitis
Sex			
Female	176 (70.68)	30 (81.08)	64 (68.82)
Male	73 (29.32)	7 (18.92)	29 (31.18)
Age			
16–25	15 (6.02)	1 (2.70)	3 (3.23)
26–35	66 (26.51)	9 (24.32)	15 (16.13)
36–45	59 (23.69)	12 (32.43)	18 (19.35)
> 45	109 (43.78)	15 (40.54)	57 (61.29)
Region of Residence			
North and Northeast	43 (17.27)	10 (27.03)	13 (13.98)
Southeast and South	72 (28.92)	4 (10.81)	30 (32.26)
Central-West	134 (53.82)	23 (62.16)	50 (53.76)

Values expressed in N (%).