



Celiac Disease in Multiple Sclerosis: A Controversial Issue

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Abstract

Celiac disease is a common immune mediated disorder elicited by gluten that may manifest with neurological symptoms independent to gastrointestinal manifestations. The real prevalence of celiac disease in multiple sclerosis is still unclear because of limited population studies, different diagnostic assessment and possible non-celiac related response to gluten free diet. Recent studies have contributed to clarify genetic and immune overlap and discrepancy between the two conditions and are discussed in this review. Diagnostic delay of CD is frequently reported especially in extra intestinal symptoms. The recognition of celiac disease in patients with multiple sclerosis is critical to avoid malabsorption, to reduce morbidity and complications related to these disorders.

Keywords

Celiac disease, Multiple sclerosis, Gluten, Anti-gliadin, Transglutaminase

Introduction

Celiac Disease (CD) is currently defined as an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy [1]. Although biopsy specimen analysis of the small bowel remains a 'gold standard' for diagnosis, serum antibodies can be measured such as the anti-gliadin (AGA), anti-reticulin, anti-deamidated forms of gliadin peptides (DGP), anti-endomysial and antitissue transglutaminase (tTG) antibodies and present different sensitivity and specificity. Currently CD has a worldwide prevalence of 0.7-2% in the general population. However, many cases are still undiagnosed. At any age, CD may be difficult to recognize because of the variability of the intestinal and extra-intestinal symptoms and signs, and the possibility of silent forms [1]. A wide range of neurological symptoms, such as ataxia, epilepsy, myelopathy and neuropathy, can occur in about 10% of CD subjects [2]. The neurological dysfunction can not only precede CD, but also be the only manifestation of CD.

Multiple Sclerosis (MS) is a complex chronic neurological disease that attacks the central nervous system, i.e. the brain, spinal cord and optic nerves, and characterized by the destruction of the myelin sheath that surrounds neurons, resulting in the formation of plaques [3]. It is estimated that more than two million people have

MS worldwide and the disease is among the most common causes of neurological disability in young adults [4]. The exact prevalence of MS is difficult to estimate because of marked geographical disparities. Europe is considered a high prevalence region for MS ($\geq 30/100,000$), containing more than half of the global population of people diagnosed with MS [4].

The first description of some clinical improvement with Gluten Free Diet (GFD), additional vitamins and minerals, in a small group of patients with MS dates back to 1974 [5]. In 1996 different neurological manifestations have been reported in CD patients [6]. Since then several authors have reported small case series of CD in MS and recently, even a more significant increased prevalence of CD has been shown in MS first-degree relatives (18%) [7].

Neurologic complications of CD have long been related to malabsorption and vitamin deficiencies, particularly B12, E, D, folic acid, and pyridoxine, which are nowadays rare and do not correlate with neurological symptoms in most patients. However, in patients with MS, malnutrition should be prevented as it has been associated with impairment of the immune system, mental function, respiratory muscle strength and increased risk of specific nutrient deficiencies [8].

The shared findings of apoptosis and immune dysregulation, autoimmune co-morbidity, such as diabetes and thyroiditis, and partially overlapping clinical symptoms would support the hypothesis of an increased prevalence of CD in MS [7].

Immune Mechanisms and Clinical Manifestations

There is an rising body of evidence showing that in MS a more complex interaction of B cells, specific antigens, antibodies, and innate immunity may determine the tissue damage involving not only myelin but also axons, cortical neurons, and nodes of Ranvier [9]. Both innate and adaptive immune responses are also implicated in the pathogenesis of CD and genetic predisposition is necessary but not sufficient to the expression of CD and associated conditions. Different environmental factors other than gluten exposure have long been considered but without any significant correlation so far.

Gluten-related antibodies at the level of the Purkinje cells, where they produce a marked inflammatory response followed by neuronal degeneration and cerebella atrophy, have been reported in CD [10,11]. An isoenzyme of transglutaminase, specifically the subtype 6, has been identified in the cerebellum of patients with CD-associated

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ataxia [12]. Anti-neuronal antibodies have been demonstrated in a population of adult patients with CD and neurological symptoms [13]. Moreover, a proportion of patients with neurological symptoms have reported clinical benefit on GFD. Conversely, other studies have not confirmed an increased prevalence of CD in patients with MS [14-18]. This discrepancy in the literature may be related to different factors: the small samples of MS population screened for CD, the heterogeneous antibodies pattern used to identify CD, the lack of intestinal biopsy, in some patients, to confirm the diagnosis of CD, the possible clinical benefit of GFD in gluten-sensitive, but not celiac patients.

The absence of gastrointestinal symptoms is not a new finding [19] but is now increasingly common in CD, and, particularly in patients with MS, cannot be used to rule out the diagnosis of CD. The cost-benefit of an early screening of CD in MS is currently unclear.

In the MS-CD patient, the interaction between MS- and CD-related inflammatory processes may result in a strong increased expression of T-bet with an amplification of Th1 immune response [20].

Lymphocytic infiltration in the cerebellum, mesencephalon, posterior columns, and peripheral nervous system has been described in CD [2]. A possible direct neurotoxic action of gluten or antigliadin antibodies has been hypothesized in genetically susceptible individuals [6]. In one pediatric study, magnetic resonance imaging detected unilateral and bilateral T2-hyperintensive white-matter lesions of different localization and degrees of intensity, varying between smaller spot and larger flat lesions, in 15 out of 75 (20%) CD patients, without a correlation with dietary compliance or neurologic or electroencephalographic abnormalities. None of these patients had neurologic symptoms at examination or a history of perinatal problems such as prematurity or asphyxia [21]. Risk factors, immune relation and prognostic value of these lesions are still unclear and need to be elucidated in additional longitudinal studies [21]. However, compared to MS, lesions in CD seem more peripherally situated and often confluent, with ataxia as a prominent feature [22].

In 1996 positive AGA antibodies were reported in more than 50% of subjects with neurological dysfunction of unknown cause, but because the diagnosis of CD was not confirmed by histological findings this “phenomenon” was labelled as “gluten sensitivity” [6]. In 2000 tissue transglutaminase was identified as specific auto-antigen of CD and nowadays tTG represents the most reliable diagnostic test for CD [1]. In the last years deamidated gliadin peptides have shown higher specificity for the diagnosis of CD compared to the “old” gliadin antibodies. All earlier studies, which select patients to submit to intestinal biopsy based on “old” AGA and EMA antibodies, are thus only partially comparable with the recent ones.

Nevertheless, positive DGP, and specifically the IgG class, may also occur in non-celiac gluten hypersensitivity which has increasingly been reported. Intestinal and extra intestinal symptoms, response to gluten free diet, and positive HLA-DQ2 (in 50% of these patients) may be present in this other disorder of the “gluten spectrum” [23], although immune (anti-endomysial and tTG negative tests) and histological features, such as normal villi and lamina propria, differentiate non-CD gluten hypersensitivity from CD [24,25]. The exact prevalence, natural history and association with neurological manifestations in this “new” entity are currently unknown. Interestingly, symptoms of non-CD gluten hypersensitivity may include abdominal pain, rash, diarrhea, tingling and/or numbness in hands and feet, fatigue, and musculoskeletal pain, headache, mental confusion, as well as more severe neurologic and psychiatric conditions including schizophrenia and cerebella ataxia [23].

The influence of MS treatment on celiac antibody expression has never been fully explored but must be considered in immune suppressed patients. Total serum IgA should be quantified in each patient because IgA deficiency, which is more common in CD compared to the general population, may cause negative IgA AGA, EMA, DGP and tTG test. Lastly, because the presence of antibodies is

Table 1: Association between CD or MS and HLA .

Disease	HLA	Encoded by
CD	DQ2	HLA-DR3-DQA1*0501-DQB1*0201 or HLA-DR11-DQA1*0505 DQB1 0301/DR7- DQA1*0201 DQB1 0202
	DQ8	DQA1*0301-DQB1*0302
MS	DR2	DRB1*1501-DQB1*0602
Sardinian MS		DRB1*0301-DQA1*0501-DQB1*0201 or DRB1*0405- DQA1*0501-DQB1*0301

Table 2: Association among CD, MS, single nucleotide polymorphism and gene regions.

Disease	Single Nucleotide Polymorphism (SNP)	Gene region	Reference
CD	rs1678542	between B4GALNT1 and OS9 genes	[31]
MS	rs703842	3' UTR of the METTL1 gene	[32]
	rs12368653	AGAP2 gene or CYP27B1 gene	[33,34]

Table 3: Association among CD, MS and other autoimmune disorders and gene variants.

Diseases	Gene variants
Crohn's disease, psoriasis and MS	IL23R, IL12B, PTGER4, JAK2, KIF21B, STAT3
CD, rheumatoid arthritis and systemic lupus	STAT4, IRF5, TNFAIP3, RGS1, CCR1, IL18RAP, IL2-IL21, UBE2L3
Type1 diabetes, MS and rheumatoid arthritis	ORMDL3, CLEC16A, IL2RA, PRKCQ, CYP27B1, IKZF1 and ETS1
CD, type 1 diabetes, rheumatoid arthritis, Crohn's disease and systemic lupus	SH2B3, PTPN2, PTPN22, PRKCQ, CTLA4, UBASH3A, IL10, IFIH1, IL2, BACH2, IL27, CD226

dependent on the presence of gluten, partial or total self-elimination of gluten from one's diet prior to testing may be investigated and excluded as may also produce a false negative test.

HLA Association

More than 95% of patients with CD share the HLA-DQ2 heterodimer, either in the cis or in the trans configuration, and most of the remainder have the HLA-DQ8 heterodimer [1] (Table 1). Conversely, non-CD gluten sensitivity is not restricted to HLA DQ2/DQ8.

MS is related specifically with HLA-DRB1*1501 allele and its associated haplotype [26], and HLA DR2 appears necessary for presenting myelin basic protein to T cells [27] (Table 1). The strongest risk factor for HLADRB1 MS patients seems a co-receptor for EBV entry into B cells. In a recent retrospective study, EBNA-1 was associated with increased odds for developing MS in analyses adjusted for age, sex, race, ethnicity, and HLA-DRB1*1501/1503 [28].

However, in some patients and in different populations, the risk allele or haplotype does not contain DRB1*1501 [29] as in Sardinians MS (Table 1) [30].

Several studies have highlighted the association of the 12q13.3-12q14.1 region with CD, type 1 diabetes, rheumatoid arthritis and MS. However, different genes most of which involved in immune functions, have been suggested [31-34]. Single nucleotide polymorphisms have been associated with CD and MS (Table 2). More recently, four clusters have been identified in multiple autoimmune diseases [35] (Table 3). Based on these preliminary results there is a limited genetic overlap (PRKCQ and IL2 loci) between MS and CD [35].

Conclusion

Currently, there is no evidence for recommending the routine screening for CD in MS. Different immune and genetic basis may represent crucial insights to explain the lack of increased prevalence of CD in MS. However, to date, all the studies investigating the association between these two diseases were statistically underpowered because of the small sample size, and a wide population study is necessary to draw a clear conclusion. In MS patients with ataxia as the prominent feature or with unclear clinical course or atypical MRI findings or

not responding to MS treatment, antibody test for CD would be recommended even in absence of intestinal symptoms. Which panel of antibodies test should be assessed (tTG only or combined with tTG6 and/or EMA or DGP) still need to be clarified in these patients. The awareness of hallmarks of the gluten related disorders is still poor. Diagnostic delay of CD is frequently reported especially in extra intestinal symptoms, increasing the rate of complications such as gastrointestinal problems, nutritional deficiency, impaired growth, delayed puberty, reproductive and autoimmune disorders, and possible malignancy or progression of neurological manifestations.

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