6

Multiple Sclerosis and Celiac Disease

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1. Introduction

Celiac disease (CD) has traditionally been thought of as a primarily intestinal disorder, and is now considered the most important autoimmune disease related to gluten intolerance (gluten-sensitive enteropathy) *(Freeman et al., 2011)*. It occurs in genetically susceptible individuals through the ingestion of gluten and is more frequent in women, as is also the case for many autoimmune diseases *(Gleicher & Barad, 2007; Invernizzi et al., 2009)*.

Gluten sensitivity (GS) is an immune-mediated disease which appears in individuals intolerant to gluten without the intestinal involvement that characterizes CD. Genetic susceptibility is less clear here than in CD. The immunopathogenesis associated with gluten is supported by the favorable response to gluten-exclusion diet *(Sapone et al., 2012)*.

Neurologic manifestations of gluten-related disorders (GRDs), with enteropathy (celiac disease) or without enteropathy (non-celiac gluten sensitivity), are frequent, their pathogenesis including an immunological attack on the central (CNS) and peripheral nervous system (PNS) leading to inflammatory lesions accompanied by neurodegenerative changes. The clinical manifestations are varied, but the most common syndromes are cerebellar ataxia and peripheral neuropathy, which can improve if they are treated early on with a gluten-free diet (GFD) *(Ford, 2009; Hadjivassiliou et al., 2010)*.

To a varying degree, GRDs are associated with other complex neurological diseases such as multiple sclerosis (MS) and neuromyelitis optica (NMO), both autoimmune demyelinating diseases of the CNS, whose evolution could be unfavorably influenced by gluten intolerance *(Marrie & Horwitz, 2010)*. The early detection of CD or GS associated with neurological manifestations caused by demyelinating diseases and their subsequent treatment with GFD could prove beneficial to the patients who suffer from them (*Hadjivassiliou et al., 2010; Hernández-Lahoz et al., 2011*).

2. Demyelinating diseases of the CNS

The family of CNS inflammatory demyelinating diseases represents a broad spectrum of disorders. MS is the most common of them, affecting more than one million people worldwide *(Hu & Luccinetti, 2009)*.

2.1 Multiple sclerosis

MS is a chronic neurological disease of unknown etiology associated with autoimmunity. Activated, potentially autoimmune, T cells cross the blood-brain barrier and produce inflammatory plaques and axonal damage in the brain, spinal cord or optic nerves. The end result is the accumulation of focal plaques of demyelination and gliosis in the CNS *(Compston & Coles, 2008)*.

MS is the most common disabling disease of the CNS in young adults. It affects about 1 ‰ of the population in western countries and is twice as prevalent in women as in men *(Fromont et al., 2010; Orton et al., 2006)*.

MS generally starts with episodes of acute neurological dysfunction followed by complete or partial remission and a symptom-free interval until the next outbreak. This relapsing-remitting form (RRMS) is the initial disease course in more than 80% of individuals with MS *(Confavreux et al, 1980; Lublin & Reingold, 1996)*.

The first relapse is usually localized in either the CNS or optic nerves. The patient displays an episode of acute neurological dysfunction, generally followed by recovery, which is known as the clinical isolated syndrome (CIS). In most cases, symptomatic, as well as previously silent demyelinating lesions, can be found through magnetic resonance imaging (MRI). After CIS, new recurrent events occur and eventually lead to more permanent neurological disabilities, and new lesions can also be detected by MRI during the asymptomatic intervals *(Miller et al., 2005; Swanton et al., 2007)*.

Some individuals have an MRI scan that is highly suggestive of MS, but have no signs or symptoms. These asymptomatic patients are referred to as having a radiological isolated syndrome (RIS) and are at risk of developing CIS and full blown MS *(Okuda et al., 2009, 2011; Ramagopalan et al., 2010; Sellner et al., 2010)*.

The diagnosis of MS requires that the symptoms and signs of CNS white-matter involvement are disseminated in time and space, as well as supportive evidence from MRI studies. Detection of oligoclonal bands of immunoglobulin G (IgG) in cerebrospinal fluid (CSF) specimens can be important to support the inflammatory demyelinating nature of CIS, and to predict the future conversion to MS (*Polman et al., 2011*).

Intravenous corticosteroid therapy is commonly the initial treatment for acute attacks of optic neuritis or encephalomyelitis. Using an experimental model of autoimmune encephalitis as a starting point, immunomodulatory and immunosuppressive therapies have proven effective in preventing relapses in RRMS patients, especially when initiated early in the course of disease *(Compston & Coles, 2008)*. Moreover, a new era in the treatment of RRMS, with oral and new parentally administered drugs, is now emerging.

However, the complex etiology of autoimmune diseases not only presents a challenge to the development and testing of new therapies, but also offers a framework that allows the identification of patients who might benefit from particular approaches.

2.2 Neuromyelitis optica

NMO (Devic's disease) is a chronic disease of unknown etiology associated with autoimmunity and is characterized by the presence of inflammatory and demyelinating

lesions in the spinal cord and optic nerves. NMO is up to nine times more prevalent in women than in men *(Wingerchuk et al., 2007)*.

Initial reports considered NMO to be a variant of MS, but more recent case series have suggested it to be a distinct disorder *(O'Riordan et al., 1996; de Seze et al., 2003)*. The combination of clinical, neuroimaging, serologic and pathologic characteristics permit NMO to be distinguished from MS.

NMO is clinically characterized by severe attacks of optic neuritis and myelitis. The attacks in NMO, unlike those in MS, commonly spare the cerebral white matter in the early stages.

MRI of the brain at the onset of NMO is typically normal (except for the optic nerve) in contrast to what happens in MS. MRI findings of the spinal cord in NMO show extensive lesions longitudinally, which characteristically span three or more contiguous vertebral segments. By contrast, in MS the lesions rarely exceed one or two vertebral segments in length.

Prominent CSF pleocytosis is a characteristic of NMO, but is rare in typical MS. Supernumerary oligoclonal bands of IgG in the CSF, signifying synthesis of intrathecal immunoglobulins, are detected in 85% of patients with MS but in only 30% of patients with NMO.

Serologic evidence of B cell autoimmunity has been observed in a high proportion of patients with NMO (*Graber et al., 2008*). The detection of NMO-IgG auto-antibody in the serum of patients is a characteristic finding of this condition and distinguishes it from other demyelinating disorders (*Lennon et al., 2004*). NMO-IgG antibody binds to aquaporin 4, which is the main channel that regulates water homeostasis in the CNS (*Lennon et al., 2005*).

Intravenous corticosteroid therapy is commonly the initial treatment for acute attacks of optic neuritis or myelitis. Plasmapheresis is used to treat patients who do not respond promptly to corticosteroid treatment (*Keegan et al., 2002; Ruprecht et al., 2004*). Maintenance immunosuppressive drugs or alternative treatment with Rituximab, a monoclonal antibody directed against the B cell marker CD20, are generally accepted strategies for reducing relapses of NMO (*Wingerchuk et al., 2005; Bomprezzi et al., 2011*).

3. Association of CD with demyelinating diseases of the CNS

CD is a common condition that affects up to 1% of the population worldwide. The diagnosis is based on the presence of characteristic lesions in small-intestinal biopsy. The genetic basis for gluten intolerance is mainly attributed to the HLA class-II locus located on chromosome 6p21. Serologic tests aid in the diagnosis of disease, although no one test is ideal (*Green & Cellier, 2007; Di Sabatino & Corazza, 2009*).

A high level of IgA anti-tissue transglutaminase-2 (tTG-2) antibody in the serum of the patients is an important serologic marker for diagnosis, and some studies have suggested a correlation with the severity of small intestinal villous atrophy (*Vivas et al., 2009*). Anti-tTG-2 antibody may be negative in the presence of partial villous atrophy or in subjects on a GFD prior to testing (*Sugai et al., 2010*).

Atypical forms of CD, i.e. without prominent gastrointestinal symptoms and with frequent extra-intestinal manifestations, are being increasingly recognized, especially over the past decade, both in adult and pediatric patients (*Roma et al., 2009; Rostami et al., 2009*).

Autoimmune disorders occur 10 times more commonly in CD than in the general population (*Catassi et al., 2010*). The association of autoimmune disorders and CD is considered to be due to a shared genetic tendency. When both occur in a patient, CD is frequently silent, and the patient is initially diagnosed with the autoimmune disease. Several autoimmune diseases may also improve with a GFD (*Green et al., 2005; Green & Cellier, 2007; Freeman et al., 2011*)

CD is around 10 times more frequent than MS. NMO is less frequent than MS, except in East Asians and other nonwhite populations worldwide. The association of CD with autoimmune demyelinating diseases of CNS, such as MS (*Ferro et al., 2008; Frisullo et al., 2008; Pengiran Tengan et al., 2004; Phan-Ba et al., 2011*) and NMO (*Bergamaschi et al., 2009; Jacob et al., 2005; Jarius et al., 2008; Matijaca et al., 2011; McNamara et al., 2011; Meyts et al., 2011*), has been described previously, generally as case reports with a small number of patients and short follow-up.

We have also described (*Hernández-Lahoz et al., 2009*) the case of a 29-year-old woman suffering from RRMS clinically with recurrent relapses of myelitis at different spinal levels, every year for three years. She had typical MS lesions in brain and spinal cord MRI-scan, oligoclonal IgG bands in CSF and delayed spinal conduction in somatosensory-evoked potentials with normal visual evoked potentials. The last relapse appeared associated with symptomatic CD with diarrhea, abdominal pain and loss of weight. She also had high titers of serum IgA anti-tTG-2 antibody, was homozygous for the HLA-DQ2 allele, and exhibited moderate villous atrophy (type 3B of Marsh) in duodenal biopsy. The patient has followed a strict GFD as single treatment for the last seven years. She regained her previous weight and maintained good health all the time. Not only did she not have any digestive disorder, which was expected, but more surprisingly she had no new neurological disorders, staying asymptomatic without suffering any further relapses to date. IgA anti-tTG-2 antibody values, since the first year on GFD, returned to normal. Gastrointestinal (GI) endoscopy, repeated two years after the onset of GFD, showed normal duodenal mucosa, without any inflammation. MRI confirmed a clear reduction of the spinal and brain lesions and probable remyelination. She remains fully asymptomatic and neurologic tests are normal.

4. Prevalence of CD in MS patients

CD and MS are considered T-cell-mediated autoimmune diseases (*Cox et al., 2010; Dørum et al., 2010; Frisullo et al., 2008*). Celiac patients do not tolerate gluten. In the lamina propia, the peptides deamidated by tTG-2 are recognized by CD4+ T cells, facilitating a large cascade of inflammatory processes that damage and eventually destroy the villous architecture of the small intestine (*Molberg et al., 2001*).

CD4+ cells are involved in the pathophysiology of MS (*Chitnis*, 2007). Regulatory T cells (Treg) from peripheral blood of animal models have demonstrated capacity to suppress various types of immune responses, including autoimmune attack against the CNS by activated effector T cells (Teff). Treg have a central role in protecting an individual from autoimmunity. MS and other autoimmune and inflammatory diseases may have an impaired Treg function and an imbalance in Teff-Treg homeostasis (*Buckner, 2010; Fritzsching et al., 2011; Vélez de Mendizábal et al., 2011*).

The anti-tTGs are auto-antibodies against enzymes, while the AGA (anti-gliadin antibody) is an antibody to a food component. The single most sensitive and specific serologic marker of CD is the IgA anti-tTG isotype 2 (over 90%). The presence of the AGA has been historically considered to be an important hallmark of CD, although lower figures for its sensitivity and specificity in comparison to IgA anti-tTG-2 have led to many people abandoning it as a marker for diagnosis (*Tofledal et al., 2010*). Furthermore, AGA may be present in other inflammatory diseases and also appear in many healthy people (*Uibo et al., 2010*).

The new test for anti-gliadin antibodies that uses deamidated gliadin peptides (DGP) instead of whole gliadin protein mixtures is more specific for detection of CD than is classic AGA (*Dahle et al., 2010*). IgG anti-DGP is now considered to have as much sensitivity and specificity as IgA anti-tTG-2 antibody test for detection of CD (*Vermersch et al., 2010; Volta & de Giorgio, 2010*).

The term 'non-celiac gluten sensitivity' has been used to describe the presence of positive AGA in patients without intestinal involvement, but with associated extra-intestinal manifestations (*Troncone & Jabri, 2011*). An immune-mediated pathogenesis, initiated by gluten, is considered in patients affected by neurologic disorders, with positive AGA and immunologic abnormalities of the CNS and PNS, especially if some have a favorable response to GFD with lower AGA titers. (*Fernández et al., 2005*).

Anti-tTG-6 antibody is the best serologic marker for assessing neurological GS, whereas antibody to tTG-3 is the best marker for dermatitis herpetiformis, but these assays are not yet available for routine clinical practice (*Stamnaes et al., 2010*).

The relationship between CD and MS in the same patient is a controversial issue in the medical literature. In two case series with a sample of more than 300 MS patients from Italy, all patients lacked specific antibodies related to CD. In these studies, however, positive antibodies were only detected in one individual of the control group. This individual appeared to be affected by CD (*Nicoletti et al., 2008; Salvatore et al., 2004*).

GS was studied in a sample of 161 MS patients from Iran, testing serum IgG and IgA AGA, and compared with a healthy control group. Neither IgG nor IgA AGA showed significant differences between MS patients and controls. Anti-tTG antibodies and histopathologic studies were negative in selected patients with positive IgG or IgA AGA results (*Borhani Haghighi et al., 2007*)

On the basis supposition that vitamin D deficiency caused by malabsortion may increase the risk of MS and high serum concentrations of 25-hydroxycholecalciferol having a protective effect against MS, a Swedish study investigated the possible relationship between CD and MS in a register of patients with diagnosis of CD between 1964–2003. The study found no increased risk of MS in patients with CD. However, the authors excluded 12 patients who had previously been diagnosed as having MS and also 4 patients in whom MS was detected in the first year of the follow-up (*Ludvigsson et al., 2007*). It is also possible that the mildest cases of MS were not diagnosed, particularly in the period preceding the introduction of MRI.

By contrast, a study from Norway in 38 MS patients found significantly higher titers of IgA and IgG AGA in the MS group in comparison to the control group ($p < 0.001$) (*Reichelt & Jensen, 2004*).

A study from Israel that sought to determine the prevalence of AGA and anti-tTG antibodies in MS patients analyzed the serum of a series of 98 MS patients compared with 140 controls. The authors found a significant increase in the titers of IgG-AGA and tTG-2 in the MS patients. Seven patients (7.1%) had a positive IgG-AGA, whereas only 2 controls (1.4%) had positive titers (p=0.03) and 4 patients (4.1%) had positive IgG anti-tTG-2 while all the controls tested were negative (p=0.02). However, IgA-AGA and tTG-2 were not significantly higher in the MS group in comparison to the control group (*Ben-Ami Shor et al., 2009*).

Our group analyzed, in a prospective and observational study, the prevalence of serologic, genetic and histologic CD markers, in a series of 72 RRMS patients from Asturias (Spain) and in their 126 first-degree relatives, compared to 123 healthy controls (*Rodrigo et al., 2011*).

Of the 72 RRMS patients, 60 (83%) were women and, among them, 32 had children. The female-male ratio was 5:1. The age of the patients ranged from 24 to 58 years. The mean duration of MS was 11 years. At the beginning of the study, the mean annual relapse rate was 1.1 and the median Expanded Disability Status Scale (EDSS) was 2 (range, 0-5). Forty-four patients (67 %) had been treated with immunomodulatory agents.

IgA anti-tTG-2 antibodies were positive (values > 2 U/ml) in 7 RRMS patients (10%) compared to 3 healthy controls (2.4%) (p=0.04). No differences were found in the frequency of HLA-DQ2 marker of genetic susceptibility for CD between the MS (29%) and control (26%) groups (p>0.5).

An upper GI endoscopy with multiple duodenal biopsies was performed on all patients included in the study. Duodenal biopsies were studied by two expert pathologists and classified according to the histologic classification for CD screening, described by Marsh in 1992 and modified seven years later by the European Pathologists Consensus Conference (*Oberhüber et al., 1999*).

The small bowel biopsies showed mild or moderate villous atrophy (types 3 A/B of Marsh) in 8 MS patients (11.1%), who were simultaneously diagnosed with CD. Of these, 7 patients showed slightly increased serologic levels of anti-tTG-2; 6 mild gastrointestinal symptoms and 1 moderate weight loss. We also found a high proportion of CD among first-degree relatives of the RRMS patients (18.6%).

All the 8 CD patients were put on a GFD, which was followed with good adherence. All of them improved considerably with respect to their gastrointestinal and neurological symptoms during the 3 years of follow-up.

5. Possible therapeutic implications

At present, MS therapy is not associated with a particular diet (*Riccio et al., 2011*). Historically the GFD has occasionally been used in MS patients and there have been anecdotal reports indicating both positive effects after its implementation (*Hafner, 1976*) as well as no benefit (*Hewson, 1984*).

In our case report, the patient has followed a strict GDF as single treatment for the last seven years and she has been in good health, without suffering any further relapses or new digestive symptoms to date. Thus, GFD appeared to 'kill two birds with one stone'.

The development of autoimmunity against multiple targets might be a secondary effect of shared genetic risk factors that predispose individuals to several autoimmune diseases (*Visser et al., 2009; Gutiérrez-Achuri et al., 2011*). In the case of patients with these two autoimmune diseases (CD and MS), we hypothesized whether addressing one of them might result in an improvement in the other. In our experience, GFD has been the most important treatment for CD, but it could potentially be useful for both diseases. The main difficulty for these patients is to follow a strict GFD for the rest of their lives.

MS and NMO patients could be good candidates for a clinical trial with a GFD, if they have had positive anti-tTG-2 IgA or anti-DGP IgG antibody tests and confirmatory villous atrophy in the duodenal biopsies. The prevalence of CD among RRMS patients in our study is higher (11.1%) than in previous studies (*Ben-Ami Shor et al., 2009; Nicoletti et al., 2008; Salvatore et al., 2004*). Therefore, we consider that in clinical practice, it would be prudent to perform testing for the early detection of CD in MS patients.

Continued exposure to gliadin for several years, starting in infancy, may not only be the main cause of activation of CD but also an additional factor that in some patients triggers other autoimmune diseases. Recent genoma-wide association studies (GWAS) in immune-mediated and autoimmune diseases have identified more than a hundred regions of the genoma with susceptibility loci to one of these common diseases. In addition, there is evidence that loci predisposing to one disease can have effects that increase the risk of the patients developing a second disease, although the risk allele for one disease may not be the same as for the other (*Cotsapas et al., 2011*).

Continued studies of these individuals with multiple immune/autoimmune disorders are necessary to help identify shared genetic susceptibility and to apply appropriate treatment strategies for patients (*Baranzini, 2009*).

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