International Journal of Celiac Disease, 2018, Vol. 6, No. 3, 76-82
Available online at http://pubs.sciepub.com/ijcd/6/3/5

DOI:10.12691/ijcd-6-3-5

Celiac Disease and Neurological Manifestations of Gluten Sensitivity. What Do They Share in Common?

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Received October 10, 2018; Revised November 12, 2018; Accepted January 04, 2019

Abstract Knowledge on the clinical, autoimmune, genetic and more recently microbiome and epigenetic interactions in celiac disease (CD) is consistently improving; however, the pathogenic mechanisms of neurological manifestations of gluten sensitivity (NMGS) and their potential relationship with CD remain unclear. Difficulties in assessing both conditions include their highly variable clinical manifestations and the insufficient sensitivity and specificities of currently available diagnostics tools. Patients with neurological manifestations that respond to gluten withdrawal may or may not present enteropathy and others having demonstrable mucosal damage may or may not respond to GFD. Current pathogenic hypotheses that may relate both conditions, the spectrum of clinical manifestations, diagnostic problems, including differences in types and subtypes of antibodies described for diagnosis and the effects of gluten-free diet are reviewed. The evidence show that decisions based on clinical data may be successful for patient management, but do not allow drawing conclusions on the relations between CD and NMGS.

Keywords: *celiac disease, neurological manifestation, gluten sensitivity*

Cite This Article: Rubén Peña, Gabriela Román, Natalia Zuloaga, and Magdalena Araya, "Celiac Disease and Neurological Manifestations of Gluten Sensitivity. What Do They Share in Common?" *International Journal of Celiac Disease*, vol. 6, no. 3 (2018): 76-82. doi: 10.12691/ijcd-6-3-5.

1. Introduction

Known manifestations of gluten related disorders have increased and today include a large range of clinical symptoms, which share gluten ingestion as a common trigger. Among these, celiac disease (CD) is the best characterized condition [1, 2, 3, 4] and is often taken for comparison [5, 6]. Gluten sensitivities other than EC are well described; such as the neurological manifestations of gluten sensitivity (NMGS) [7]. Clinical, autoimmune, genetic and more recently microbiome and epigenetic interactions play relevant roles in CD pathophysiology, but the mechanisms underlying those other conditions characterized by gluten sensitivity are still poorly understood [8,9]. Understanding the relationship between CD and NMSG is challenging because systematic studies on NMGS are scarce and most evidence is based on clinical reports. Screening/diagnostics tools (mainly blood antibodies and small intestinal biopsies) currently available are not fully sensitive nor specific. In both conditions, the spectrum of clinical presentations is enormous and equally relevant, most NMGS (like migraine, depression) and gastrointestinal symptoms (as abdominal distention, diarrhea, and constipation) are quite frequent in the general population. This makes current literature on these topics hardly comparable and biased by the centers and specialists reporting data.

2. Methods

We reviewed and contrasted, from the gastroenterology perspective, the evidence about CD and NMGS available in Medline, Cochrane and Scielo, including articles in English and Spanish and others referred to in the primary article. Papers that provided new evidence or discussion were included in the analysis and those corroborating previously described information were excluded. Data was summarized to include the diverse clinical manifestations, pathophysiologic hypotheses, most frequent diagnostic problems and the effects of gluten-free diet (GFD).

3. The Spectrum of Celiac Disease

Described in the '50s, CD was originally thought to be a rather infrequent condition of childhood characterized by intense diarrhea and abdominal distention, growth failure and malnutrition [10,11]. Development of techniques that measured antigliadin antibodies (AGA) improved the diagnostic search for CD, but subsequent discovery of the more sensitive and specific antiendomysial (EMA) and

anti-transglutaminase 2 (TTG) antibodies led to discontinue the use of AGA [12,13]. Application of EMA and TTG greatly improved the search and diagnosis of CD, widening the limits of what we understand by CD and gluten related disorders. Today, CD is conceived as an autoimmune disorder affecting ~1% of the general population, triggered by gluten ingestion in genetically susceptible individuals; which appears at any age, presents with variable (gastrointestinal and extra intestinal) symptoms, with EMA, TTG and/or deamidated gliadin peptides (DGP) typically present in blood and also variable degrees of damage in the small intestinal mucosa [1,14]. When classifying CD, silent presentations refer to lack of symptoms and typical histological damage and potential CD to positive antibodies with normal small intestinal mucosa. Non-celiac gluten sensitivity (NCGS) is diagnosed when antibodies and biopsy are negative for CD and wheat IgE is within normal levels, while symptoms clearly decrease after dietary gluten withdrawal and relapse on gluten challenge [5,6]. Finally, wheat allergy is diagnosed when immune mechanisms mediated by IgE are demonstrated, [15]. A large proportion of patients respond to GFD, although symptoms of different intensity and variable degrees of mucosal damage may remain in some patients. At the end of this spectrum is refractory CD, a severe and infrequent clinical condition in which patients do not respond to GFD and often need steroids and immune suppressors [16]. Follow-up consists of periodic measurement of blood autoantibodies, assuming that elimination of dietary gluten abates the autoimmune phenomena. However, these antibodies poorly correlate with the clinical and histological course of the disease; this sometimes results in that treatment must rely on clinical assessment [17,18]. Periodic or repeated small intestinal biopsies may show histological damage, which not always correlate with the clinical course of CD [19]. Similarities and differences between the celiac spectrum and NMGS is discussed in the following paragraphs.

4. Neurological Manifestations of Gluten Sensitivity

The first description of biopsy confirmed CD associated with neurologic manifestations was published in 1966 [7]. In the ‘90s and using AGA and duodenal biopsies, CD was described as being 16 times more frequent among patients with ataxia than in general population [20]. There is no confirmed prevalence of NMGS as figures available depend on the center reporting information. Patients with neurologic manifestations among celiac patients followed in gastroenterology clinics have been reported at 12 to 22.5%, which is similar or higher than figures published for several other autoimmune disorders also associated with CD [21,22,23,24]. As in CD, clinical presentations are variable; patients with neurological manifestations that respond to gluten withdrawal may or may not present enteropathy and others having demonstrable mucosal damage may or may not respond to GFD [25]. An additional confounding factor is the laboratory tests performed for patient’s evaluation, because the type and subtype of antibodies measured to demonstrate autoimmunity also influence the results [25] (see below).

5. Pathophysiology

Although still not completely understood, it is widely agreed that genetic factors, the intestinal microbiome and autoimmunity are implicated in CD pathogenesis [26]. Partially digested proline rich gliadin peptides derived from dietary gluten pass through the epithelium and reach the lamina propria (Figure 1). There, TTG forms a complex with them, resulting in greater affinity for HLA-DQ2 o HLA-DQ8 pockets in the antigen presenting cells. During this process, antibodies are formed against TTG2, gliadin and actin, through mechanisms still unclear. Both the antigens and antibodies may pass to blood circulation and contribute to the appearance of extra intestinal manifestations; however, this line of thought is not enough to explain manifestations originating in the central nervous system (CNS). Both innate and adaptive immune responses are necessary for the appearance of typical celiac intestinal mucosal lesions, although how these mechanisms interact in the intestinal mucosa and elsewhere is not completely elucidated [27].

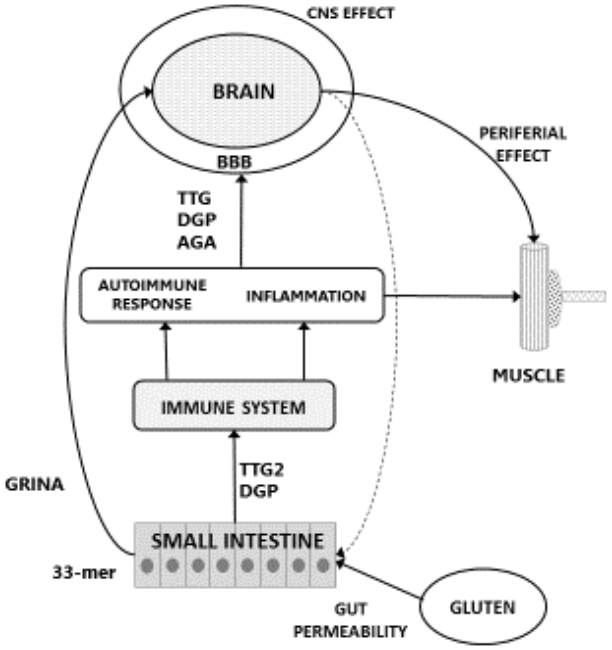

Figure 1. Brain-intestinal axis and gluten related disorders.

5.1. Genetics

This represents a major risk factor for CD, including HLA, non-HLA genes and gene sets identified by genomic studies [28]. HLA-DQ2 and DQ8 are the best described and for this reason, they were studied in patients with NMGS. In Europe, more that 90% of celiac patients carry HLA- DQ2.5 (DQA1*05-DQB1*02) variants. Most of the remaining ones are HLA-DQ8 (DQA1*03-DQB1*0302). In South America, distribution of HLA- DQ2 and DQ8 is different. HLA-DQ2 is present in 54% of celiac patients while HLA- DQ7 and DQ8 in 23.5% and 21.5%, respectively [29]. Studies from Argentina and Brazil also describe regional variations in HLA distribution [30,31,32]. In recently described NCGS studies, HLA DQ genotypes proved not different from those described in general population, but some evidence suggest that innate

immunity may participate in its pathophysiology [27]. Celiac patients with NMGS assessed in a gastroenterology clinic, showed that 17% of them carried HLA-DQ8 [33].

5.2. Malabsorption Syndrome and Inflammatory Processes

The first patients described with NMGS were malnourished and presented several nutritional deficiencies. This led to hypothesize that their neurological alterations were due to vitamins and other micronutrient deficiencies, secondary to malabsorption syndrome [20]. Current evidence however, does not support this as today several patients with NMGS do not present nutritional deficiencies and enteropathy may be absent.

5.3. Purkinje Cell Involvement

Cerebellar cortex post mortem studies in ataxic patients show patchy loss of Purkinje cells, while in cerebellar white substance astrocytic gliosis, neutrophils vacuolization and lymphocytes T infiltration is described [25]. This and perivascular infiltrate with inflammatory cells suggest immune participation. Experimental evidence show that antigenic epitopes in Purkinje cells and other cerebellar cells may cross-react with gluten peptides and also, in rats, AGA antibodies *in vitro* may be reactive against human Purkinje cells [25].

5.4. Tissue Transglutaminases

Different types of these enzymes are involved in gluten ataxia. TTG6 is postulated as potential antigenic target in the brain [34]. These antibodies are frequent in patients with gluten ataxia and often disappear after GFD (Figure 1). IgA and TTG6 deposits in the cerebellum, both in perivascular muscle layers and cerebellum tissue proper have been described. Perivascular changes reflect inflammatory processes that may modify the blood brain barrier (BBB); this possibility is of paramount importance because it would allow gluten antigens and/or antibodies present in blood to penetrate the CNS. It is not clear how targeting TTG2 or TTG6 is decided and which one triggers symptoms in genetically predisposed patients [35]. Although TTG6 positivity is significantly more frequent among celiac patients than controls, its comparison between CD and NMGS is not yet clear [50].

5.5. Permeability

Altered intestinal permeability is thought to be at the basis of CD pathophysiology. This hypothesis was recently tested in rats expressing two copies of Zonulin gene (HP2) [36]. Animals showed down regulation of JAM3 and Claudin 8 in intestine with diminished expression of Claudin -1, -3, -5 and -12 in the rat's brains, suggesting that permeability was altered in both organs (Figure 2). When the same animals were subsequently administered dextran sodium sulfate to induce colitis, wild type animals showed changes in the intestine and brain barriers similar to those observed in HP2 animals at the basal conditions.

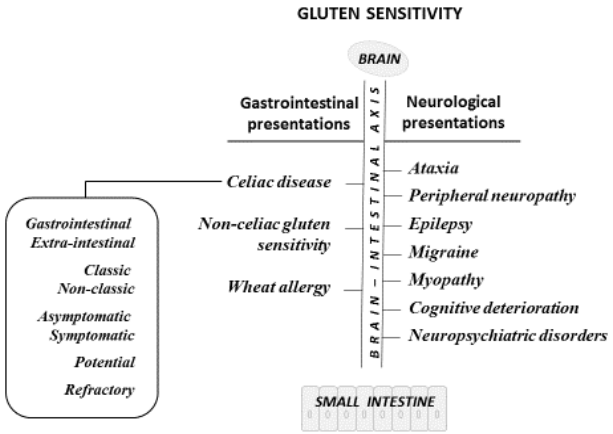

Figure 2. Gastrointestinal and neurological manifestations of gluten sensitivity

5.6. The GRINA Theory

An additional hypothesis to explain gluten actions is based on the homology of 33-mer derived from gliadin and human protein GRINA, a component of glutamate NMDA- receptor [37]. This peptide is one of the main molecules responsible for adaptive immune responses against gluten and is able to interfere with the usual gluten interactions due to the homology of its N-terminal region. If confirmed, this hypothesis could clarify several of the extra intestinal disorders that the immune/genetic model currently in use cannot explain. However, there is no evidence relating the GRINA protein and NMGS.

6. Clinical and Diagnostic Problems

6.1. Celiac Disease

Clinical presentation of CD varies from asymptomatic to symptomatic and symptoms may be gastrointestinal or extra intestinal (Figure 2). While CD is characterized by enteropathy detected by duodenal biopsies [1,3], enteropathy is not a prerequisite for the diagnosis of NMGS [20,25]. Current international criteria indicate that diagnosing CD requires measuring blood IgA levels, IgA-TTG and small intestinal biopsies. Clinical guidelines and most authors also accept measuring other antibodies, like IgA anti-endomysial antibodies (EMA) and IgA/IgG deamidated gliadin peptides (DGP). Diagnostic problems have always been strongly influenced by the fact that both in gastrointestinal and neurological presentations, diagnostic antibodies are not entirely sensitive and specific. EMA and TTG2 are good markers detecting enteropathy, but they are often negative in patients with NMGS. IgA- and IgG- AGA, which are no longer used for CD assessment, are present in a proportion of patients with NMGS [35]. From the gastroenterological perspective, there is consensus that only IgA-TTG should be measyres, leaving IgG-TTG for patients who prove to be IgA deficient [38,39]. NMGS presentations tend to differ and their gastrointestinal symptoms often do not guide diagnosis; their AGA are frequently positive; isoforms of tissue transglutaminase like TTG6 may be positive, while

antibodies against TTG2 may be negative [35]. Organ specificity has led some authors to propose that assessment of NMGS should include measurement of not one but a set of antibodies, including TTG2, TTG3, TTG6, AGA and IgA/IgG DGP [40].

6.2. NMGS

Neurological symptoms may present as atypical CD or as a separate entity, in which case the response to GFD is relevant for diagnosis. This contrasts with current criteria for CD management, which strongly advise to avoid diagnosis based on clinical indicators and response to GFD. In children, it was recently reported that CD autoimmunity makes a difference on the clinical neurological behavior of children [41]. In a large prospective cohort of children assessed at 3.5 years, mothers unaware of their child's autoimmune status reported more frequently that they were anxious/depressed (P = 0.003), presented more aggressive behavior (P = 0.03) and sleep problems (P = 0.02) compared with reports of children without CD autoimmunity (n = 3651) [41]. The most frequent manifestations of NMGS are briefly reviewed below.

6.2.1. Ataxia

This is the most frequently described neurological manifestation associated with CD. It may or may present intestinal symptoms. TTG's detected in BBB capillaries suggest the participation of transglutaminases. Using TTG6 antibodies, up to 76% of patients with gluten ataxia (GA) have proved positive for this marker [42].

6.2.2. Peripheral Neuropathy

Being the second most frequent neurological manifestation associated with CD, it is frequently described in adults [43], although a case of Guillain-Barre was recently reported in a 23-month-old child, whose symptoms responded to GFD [44]. Among patients with peripheral neuropathy, TTG2 were positive in 21% [45], while among celiac patients neuropathy was described at 2.5-8% [46]. Comparing 26 celiac patients on well-controlled GFD with 23 patients with gastro esophageal reflux, 23.1% and 4.3% showed chronic axonal neuropathy, respectively [43].

6.2.3. Epilepsy

Among celiac patients, epilepsy has been described at 0.8-6% [47], but some studies have not demonstrated the association [48]. A meta-analysis in children showed a relative risk of 2.1 for celiac patients to develop epilepsy and 1.7 for epileptic patients to develop CD [49]. Interestingly, 43% of 7590 celiac patients showed persistent flattened mucosa and this was associated with low risk of epilepsy (HR 0.61, CI 0.38-0.98) [50]. In contrast, association of epilepsy with intracerebral calcifications and CD is strong [51,52]. The response to diet seems related to the duration of epilepsy before diagnosis [53]. In a recent assessment of 113 epileptic patients in Iran, CD was demonstrated in seven (EMA and biopsy positive) and epilepsy was controlled by GFD in six [54].

6.2.4. Migraine

In idiopathic adult migraine CD was diagnosed in 4.4% in comparison to 0.4% among blood donors (P<0.05). [55]. In children with headache, 2% were diagnosed CD instead of the 1.2% described in general population (P= 0.034) [56]. However, up to date routine screening for CD is not recommended in children with migraine [57]. Whether associated or not, CD seems to include CNS disturbances; 73% adult untreated celiac patients presenting classical CD and no neurological/psychiatric disorders, showed at least one hypo fused cerebral region by PET scan in comparison to 7% in treated celiac patients and none in controls (P=0.01) [58].

6.2.5. Myopathy

This rare manifestation related to gluten sensitivity is described mainly in adults and adolescents that suffer proximal/distal weakness and inflammatory myopathy by muscle biopsy [59,60]. Proximal myopathy was described in a 5 year old celiac child, who after two month treatment with GFD showed clear nutritional improvement and recovered unsupported walk [61].

6.2.6. Cognitive Deterioration and Neuropsychiatric Disorders

Neurological symptoms and mental decline in elderly persons is often referred to as "old age", but diagnosis of CD is increasing in this group of patients [62,63]. Evidence shows that a proportion of elderly patients clearly improve cognitive capacity after GFD [64 65].

6.2.7. Psychiatric Manifestations

Depression, bipolar disorder, apathy, anxiety, irritability, schizophrenia, attentional deficit and sleeping disorders also have been described in association with CD [66-70]. Available evidence suggests that GFD for extended periods of time may help resolve some but not all the clinical manifestations [71].

7. GFD as Treatment of CD and NMGS

The widely different responses to GFD illustrates the great variability of sensitivity to gluten in humans, both in the gastrointestinal and nervous systems. Most celiac patients on GFD experience relevant relief of their symptoms, autoantibodies significantly decrease, and mucosal histology returns to normalcy or greatly improves. A proportion of celiac patients though, remain symptomatic and their positive antibodies and/or intestinal histological lesion persist despite GFD. The same variability is observed in NMGS.

Lack of tools to assess adherence to GFD and great variability of gluten sensitivity in CD and NMGS are the most relevant issues that difficult assessing treatment efficacy. Neither the length of time needed to induce positive antibodies nor the gluten dosages that induce clinical/blood responses are known. Why some types and subtypes of transglutaminase participate in the responses to gluten and not others is not clear either. It is interesting that the presence of TTG6 correlates with time of exposure to gluten and antibodies decrease or disappear during GFD [72]. Many NMGS studies do not control adherence to GFD and do not measure antibodies during follow-up, hampering proper data interpretation. All this means that management of these conditions often relies on

clinical assessment, which emphasizes the need for a specialist to take responsibility for the diagnosis and treatment. Decisions based on clinical data may be successful for patient management, but do not allow drawing conclusions on the relationship of CD and NMGS. One also must keep in mind that, although the effects of GFD may differ, a percentage of NMGS patients do improve with it.

8. Discussion

CD and NMGS appear clearly associated, but the frequency of association and shared pathogenic mechanisms remain unclear. Current evidence suggests that NMGS should be investigated in celiac patients having neurological symptoms of unclear origin and/or do not respond to routine treatment. From a neurological perspective, CD should be considered in patients with symptoms of unclear origin, which are described in association with CD or when the clinical course is not as expected. One must remember though that following GFD is difficult, expensive, significantly modifies quality of life and may add nutritional risks to the patient; therefore, it should not be prescribed without solid bases.

Antibodies against transglutaminases and deamidated gliadin peptides are useful and the best currently available diagnostic tools for CD; however, the role of AGA and TTG6 seem relevant in NMGS. Not knowing what triggers one type/subtype of antibodies makes difficult deciding which one to choose in clinical practice. Health systems restraints (economic and others) makes the idea of routinely measuring an extended series of antibodies impractical. Patients with neurologic manifestations that do not respond to GFD evoke celiac patients with refractory CD or those that remain symptomatic despite strict GFD. Also, NMGS patients with normal biopsies but good response to GFD remind to NCGS. The relationship between CD and NMGS will remain open to discussion until methods for diagnosis and measuring adherence to diet improve.

Conflict of interest

Authors have no ethical conflicts to disclose, nor conflicts of interest to declare. All authors made equal substantial contributions to the paper and they all approved the final version.

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