Neurological Dysfunction in Coeliac Disease and Non-Coeliac Gluten Sensitivity

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OBJECTIVES: Non-coeliac gluten sensitivity (NCGS) refers to patients with primarily gastrointestinal symptoms without enteropathy that symptomatically benefit from gluten-free diet (GFD). Little is known about its pathophysiology, propensity to neurological manifestations, and if these differ from patients with coeliac disease (CD). We investigated the clinical and immunological characteristics of patients presenting with neurological manifestations with CD and those with NCGS.

METHODS: We compared clinical, neurophysiological, and imaging data of patients with CD and NCGS presenting with neurological dysfunction assessed and followed up regularly over a period of 20 years.

RESULTS: Out of 700 patients, 562 were included. Exclusion criteria included no bowel biopsy to confirm CD, no HLA type available, and failure to adhere to GFD. All patients presented with neurological dysfunction and had circulating anti-gliadin antibodies. Out of 562 patients, 228 (41%) had evidence of enteropathy (Group 1, CD) and 334 (59%) did not (Group 2, NCGS). The most common neurological manifestations were cerebellar ataxia, peripheral neuropathy, and encephalopathy. There was a greater proportion of patients with encephalopathy in Group 1 and with a greater proportion of neuropathy in Group 2. The severity of ataxia did not differ between the two groups. Patients in Group 1 had more severe neuropathy. All patients from both groups responded to gluten-free diet. Anti-tissue transglutaminase (TG2) antibodies were found in 91% of patients in Group 1 and in 29% of patients in Group 2. Comparison between those patients in Group 2 with HLA-DQ2/DQ8 and those without as well as those with positive TG2 compared with those with negative TG2 antibodies identified no differences within these subgroups. Serological positivity for TG6 antibodies was similar in the two groups (67 and 60%).

CONCLUSIONS: The neurological manifestations of CD and NCGS are similar and equally responsive to a GFD suggestive of common pathophysiological mechanisms.

INTRODUCTION

Gluten-related disorders (GRDs) represent a spectrum of diverse clinical manifestations sharing a common trigger, the ingestion of gluten (1). The most widely recognized and best-characterized disease within this spectrum is coeliac disease (CD), also known as gluten-sensitive enteropathy.

Classic presentations of CD such as abdominal bloating, weight loss, diarrhea, anemia, and malabsorption are no longer the norm and patients can present with minimal or no gastrointestinal symptoms and diverse extraintestinal manifestations affecting other organs such as the skin and the nervous system (2,3). Although the presence of enteropathy, defined by the triad of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, remains the cornerstone of the diagnosis of CD, the diagnosis of the whole spectrum of GRDs is problematic. This is particularly the case for the relatively new entity belonging to the spectrum of GRDs, non-coeliac gluten sensitivity (NCGS). NCGS is currently defined by clinical evidence of improvement.
The validated diagnostic approaches. Gluten ataxia is unclear at present and awaits the development of (9,10). However, the extent of overlap between NCGS, DH, and expressed TG, have been found in patients with gluten ataxia. Nal manifestations, have been identified but are not yet in general directed at autoantigens likely to be responsible for extraintestinal manifestations seen in the context of CD, such antibodies will usually be absent in patients with NCGS. This may reflect the absence of detectable levels of circulating antibodies in some cases where the immune response is distant from the gut (e.g., cerebellum in gluten ataxia). Anti-gliadin antibodies (AGA) may appear to respond to GFD may be susceptible to develop enteropathy, without enteropathy, who also have the HLA-DQ8, and yet respond to a GFD (6). The reasons behind such differences in the gut response remain unknown. Currently, it also remains unclear which serological markers alone or in combination should be used in diagnosing the whole spectrum of GRDs, and in particular NCGS (7). Although some markers such as anti-tissue transglutaminase (TG2) autoantibodies detected as anti-endomysium antibodies or by ELISA (anti-TG2 antibodies) are sensitive and specific in diagnosing CD, such antibodies will usually be absent in patients with NCGS. This may reflect the absence of detectable levels of circulating antibodies in some cases where the immune response is distant from the gut (e.g., cerebellum in gluten ataxia). Anti-gliadin antibodies (AGA) may be an indicator of NCGS as up to 50% of such patients presenting to gastroenterologists have detectable circulating levels, primarily of IgG AGA (8). More specific markers, i.e., antibodies directed at autoantigens likely to be responsible for extraintestinal manifestations, have been identified but are not yet in general use. Antibodies against TG3, an epidermal TG, have been found in patients with DH, whereas antibodies against TG6, a brain expressed TG, have been found in patients with gluten ataxia (9,10). However, the extent of overlap between NCGS, DH, and gluten ataxia is unclear at present and awaits the development of validated diagnostic approaches.

The use of the HLA type as an aid in the diagnosis has also been advocated given that over 95% of patients with CD have the HLA-DQ2, and the remainder having HLA-DQ8. HLA type, however, cannot be interpreted in isolation as DQ2 is found in up to 25% of the healthy population, of which only a fraction will ever develop GRDs. Furthermore, while there is over-representation of DQ2 in patients with NCGS, a significant minority do not have the HLA-DQ2 or -DQ8 and yet appear to respond to a GFD. It is plausible that patients who have serological evidence of sensitivity to gluten without enteropathy, who also have the HLA-DQ2 or -DQ8, and appear to respond to GFD may be susceptible to develop enteropathy with ongoing exposure to gluten (11).

Our research into the neurological manifestations of GRD started 20 years ago. The presence or absence of enteropathy did not influence our diagnosis as these patients had no clinical features, either gastrointestinal or neurological, to distinguish between those with and those without enteropathy and had no explanation other than gluten sensitivity for their neurological problem.

Here we present the spectrum of neurological manifestations seen in the context of NCGS and we compare this with neurological manifestations seen in the context of CD (with neurological presentation). The aim was to tease out any potential differences between these two groups that may imply different pathophysiological mechanisms being responsible depending on the presence or not of enteropathy.

METHODS

We undertook a retrospective analysis of all consecutive patients presenting with neurological dysfunction related to gluten sensitivity, to a neurology clinic (Neuroscience Department, Royal Hallamshire Hospital, Sheffield, UK), with an interest in neurological manifestations of GRD for 20 years between 1994 and 2014. No alternative etiology for their neurological dysfunction was found despite extensive investigations. All patients had been clinically assessed on several occasions and almost all remained under active follow-up on a six-monthly or yearly basis. All patients included had detectable circulating AGA (IgG and/or IgA) at baseline as this was the only serum marker for gluten sensitivity available in 1994. Additional immunological markers (anti-endomysium antibodies and TG2 IgA antibodies) were assessed after they became locally available. All the serological testing was carried out at the regional clinical immunology lab. TG6 antibody testing was undertaken as previously described in some but not all patients as this test became available in 2008 (12) TG6 testing is not as yet readily available and such testing was undertaken in the investigators lab. All patients underwent duodenal biopsy, HLA typing, and were offered GFD (irrespective of the presence or absence of enteropathy). All patients were reassessed clinically and with repeat brain imaging including magnetic resonance spectroscopy of the cerebellum (for patients with gluten ataxia) and magnetic resonance imaging of the brain in gluten encephalopathy or neuropathy for patients with gluten neuropathy. All patients included had evidence of clinical and/or imaging and/or neuropathological improvement on repeat assessments. Details of the methodology for such assessments (neuropathology, magnetic resonance spectroscopy, and clinical assessment of the ataxia) has been described in detail elsewhere (6,13,14). The above investigations and follow-up represent our normal clinical practice in caring for such patients.

The patients were separated into two groups based on the presence or absence of enteropathy. Group 1 consisted of all patients with enteropathy (triat of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes) on biopsy (CD). Group 2 consisted of patients without enteropathy (NCGS). Group 2 was further subdivided into those patients with the HLA-DQ2 or -DQ8 (Group 2a) and those patients with HLA other than DQ2 or DQ8 (Group 2b). We also compared those patients in Group 2 with circulating TG2 antibodies with those without circulating TG2 antibodies.

Planned comparisons included the age of onset of symptoms, the prevalence of HLA subtypes and antibodies in the comparator groups. The frequency of dichotomous variables was compared using the \( \chi^2 \) test. Means of interval data were compared using Student’s \( t \)-test, Fisher’s exact test, or analysis of variance where parametric or Kruskal–Wallis analysis of variance if non-parametric.

RESULTS

Comparison of CD (Group 1) vs. NCGS (Group 2)

Between 1994 and 2014, a total of 700 patients have been seen and assessed in a neurology clinic specializing in gluten...
sensitivity. Out of these, 562 patients were included in this report. The remaining patients were excluded for the following reasons: refused intestinal biopsy, HLA type not available, non-compliant with GFD with persistently positive serology, neurological manifestation developed, and patient referred after the diagnosis of CD was made (total of 139 patients). Of the 562 patients included in this report, 228 (41%) had evidence of enteropathy on duodenal biopsy (Group 1). Group 2 consisted of 334 patients (59%) with normal biopsies (NCGS). The mean age at the onset of neurological symptoms in Group 1 was 53 years (range 13–90) and in Group 2 it was 57 years (range 14–87). Patients in Group 1 developed neurological symptoms significantly earlier than Group 2 (P<0.01 by Kruskal–Wallis one-way analysis of variance). The mean age at diagnosis of CD of patients in Group 1 was 52.6±15.3 years. This compared with a mean of 43.8±15 years for patients diagnosed with CD presenting to the gastrointestinal department (P<0.0001 by Student’s t-test). The mean duration of the neurological symptoms before the diagnosis of gluten-related disease was not significantly different among the two groups (P=0.06 by analysis of variance).

**HLA type**

As in the case of patients with classical CD with gastrointestinal presentation, the HLA-DQ2 (DQA1*05:01–DQB1*02:01) was present in 214/228 (94%) of all patients in Group 1 and DQ8 (DQA1 03:01–DQB1 03:02) in 8/228 (4%). There were four patients with biopsy-proven enteropathy who had only one of the DQ8*01 alleles.

In Group 2, 148/333 (44%) of patients had the HLA-DQ2 and 60 (18%) had the HLA-DQ8. The prevalence of the HLA-DQ2 or -DQ8 in Group 2 was therefore 62%. The remaining patients had neither HLA-DQ2 nor -DQ8. All but six of these patients had the HLA-DQB1*06 or -DQB1*05 (both come under the umbrella of DQ1).

**Type of neurological manifestation per group**

In Group 1 (228 patients), the most common neurological manifestations were cerebellar ataxia 41%, followed by peripheral neuropathy 30% (of which 80% had sensorimotor axonal length-dependent symmetrical neuropathy and 20% had sensory ganglionopathy) and encephalopathy 21%. Less common manifestations included ataxia with myoclonus 11, myopathy 9, myelopathy 6, stiff person syndrome 3, neurromyotonia 1, and chorea 1 (some patients had more than one manifestation).

In Group 2 (334 patients), the most common neurological manifestations were peripheral neuropathy 54% (of which 69% had sensorimotor axonal length-dependent symmetrical neuropathy and 31% had sensory ganglionopathy), followed by cerebellar ataxia 46% and encephalopathy in 10%. Less common manifestations included myopathy 8, myelopathy 6, stiff person syndrome 5, chorea 3 and myoclonic ataxia 2, and epilepsy with occipital calcifications 1 (some patients had more than one manifestation).

Overall, the prevalence of ataxia was similar in the two groups, but there was an over-representation of encephalopathy in Group 1 and of neuropathy and ganglionopathy in Group 2 (P=0.002 by χ² test). Figure 1 summarizes the frequency of the neurological manifestations within the two groups.

**Anti-gliadin antibodies**

In Group 1, the total number of patients with circulating IgG AGA was 78%, IgA AGA was 65%, and with 43% having both circulating IgG and IgA (Table 1). In Group 2, 68% had circulating IgG AGA, 53% for IgA and 21% for both. We compared these figures with 100 patients with newly diagnosed CD who presented to gastroenterology clinics (classic CD). In this group, 88% had IgG AGA, 75% IgA, and 63% had both. While by definition Groups 1 and 2 had to have circulating AGA to be included (i.e., 100% positivity), in the case of the 100 patients with newly diagnosed CD presenting to gastroenterologists, the total percentage with AGA positivity was 82%. Table 1 summarizes the above findings.
Anti-TG2 autoantibodies
Baseline TG2 IgA antibodies were available in some but not all the patients included, as the availability of the assay for these antibodies was limited at the start of this study. In Group 1, 105/115 (91%) of patients had circulating antibodies against TG2 as compared with 67/229 (29%) in Group 2. The proportion of patients positive for TG2 IgA antibodies who also had biopsy-proven CD presenting to the gastroenterology department was 97% (based on 100 consecutive patients). This illustrates, as expected, that there is a high degree of correlation between enteropathy and circulating anti-TG2 antibodies. Table 1 summarizes the above findings.

Anti-TG6 autoantibodies
The availability of TG6 antibody analysis/testing was limited as TG6 autoantibodies were not discovered until 2006, and their importance in neurological manifestations of GRD was not established until 2008. Testing for TG6 was therefore carried out in a smaller group of patients from each group and baseline samples were not available in all cases. Patients without baseline analysis and subsequently testing negative were excluded given that they were on GFD and hence no clear conclusion could be drawn. In Group 1, 36/54 (67%) of patients had circulating TG6 (IgG and/or IgA) antibodies. In Group 2, 68/114 (60%) of patients had circulating TG6 antibodies. The prevalence of TG6 antibodies in patients with newly diagnosed CD presenting to gastroenterologists was 38/100 (38%). There was a significant difference in the prevalence of TG6 between the neurology groups and the patients with CD presenting to gastroenterologists (P<0.01 χ² test). Table 1 summarizes the above findings.

Severity of neurological manifestations per group
For the purpose of comparing the severity of the neurological manifestations between each group, we concentrated on the two most common types of manifestations, gluten ataxia and gluten neuropathy. The severity of ataxia was assessed at presentation, using a simple clinical rating scale: mild (patient able to walk unaided), moderate (patient needs walking aids/support to be able to walk), and severe (patient is wheelchair bound) (15). In Group 1, 69% of patients had mild ataxia, 17% moderate, and 14% severe. In Group 2, 77% had mild, 15% moderate, and 8% severe. There were no significant differences between the two groups.

The severity of neuropathy was assessed using neurophysiological parameters (neuropsychological abnormalities confined to lower limbs, mild, involvement of arms but sparing radial nerve, moderate, involvement of radial nerve as well, severe). In Group 1, 27% had mild, 40% moderate, and 33% severe neuropathy. In Group 2, 42% had mild, 22% moderate, and 36% severe neuropathy. Mild neuropathy was more common in Group 2 with moderate and severe neuropathy being more common in Group 1 (P<0.01 by χ² test). The above observations are summarized in Figure 2.

Group 2 (NCGS) comparison between patients with positive and negative TG2 autoantibodies and those with HLA-DQ2/DQ8 vs. those without
We also performed a comparison between those patients in Group 2 with (67) and those without (162) TG2 antibodies. The rationale for this was to establish if the presence or absence of such antibodies had any bearing on such neurological manifestations. We found no significant differences in the age at onset of neurological manifestations between those with and those without TG2 antibodies (56.7±16.3 vs. 56.3±14.4 years). Similarly, there were no substantial differences in the type and severity of neurological symptoms (Figure 3). Finally, we also compared those patients with the HLA-DQ2 and -DQ8 vs. those without. We again did not find any differences between the two subgroups (Table 1).

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<th>Table 1. Summary of clinical and serological characteristics of the different groups</th>
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<td><strong>AGA, anti-gliadin antibodies; CD, coeliac disease; Ig, immunoglobulin; N/A, not applicable; NCGS, non-coeliac gluten sensitivity; TG, transglutaminase.</strong></td>
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DISCUSSION

This retrospective review of probably the largest cohort of patients presenting with neurological manifestations of GRD suggests that there are no clear distinguishing neurological features between those patients with CD and those with NCGS. Furthermore, the spectrum, severity, and response to GFD of these neurological manifestations were very similar between the two groups with some minor exceptions: gluten encephalopathy was more commonly associated with enteropathy, whereas neuropathy and ganglionopathy were less commonly associated with enteropathy. In terms of severity, patients in Group 1 tended to have a more severe neuropathy than those in Group 2. Irrespective of these differences, the neurological manifestations in both groups were equally responsive to a GFD. We have also previously shown that a subgroup of patients with gluten ataxia and myoclonus were more likely to belong to Group 1 (i.e., had enteropathy) and often had refractory CD (16). We have previously reported the beneficial effect of GFD in patients with gluten ataxia and gluten neuropathy (6,13). In those studies, we again showed that the benefit of the diet was independent of the presence of enteropathy.

NCGS belongs to the spectrum of GRD, but the pathogenesis, unlike CD, remains unclear. Involvement of innate immunity has been proposed (17). It is as yet unclear if the antigenic stimulus relates to gluten peptides or another component of wheat, e.g., amylase trypsin inhibitors (18).

However, the mucosal cytokine profile after short-term gluten challenge observed in a recent study also implicates the adaptive immune system and this notion is also consistent with the AGA response seen in NCGS (19). Support for a role for the adaptive immune system also comes from another recent study showing that a significant number of patients with CD (29%) and NCGS (29%) develop other autoimmune disorders when compared with patients with irritable bowel syndrome (4%) (20).

The role of autoimmunity in CD is well established with a recognized target autoantigen in the form of TG2. This is true for DH where the target antigen is TG3, an epidermal TG (9). We have previously shown that patients with gluten ataxia appear to have an immunological response against a primarily brain expressed TG, TG6 (12). All three TGs are capable of deamidating disease-relevant gliadin peptides and form thioester complexes with gliadin peptides, and therefore form entities that drive T- and B-cell responses, respectively (21). The prevalence of TG6 autoantibodies in the two groups was comparable (67% and 60%, respectively, in Groups 1 and 2). This is in contrast to what was observed with TG2 antibodies that were more prevalent in the group with CD compared with NCGS (91% and 29%, respectively). This observation suggests that the immunological trigger in neurology patients is distinct. Unlike CD that is characterized by TG2 overexpression and activity in the intestinal mucosa, which drives the immunological response, such abundance and overwhelming activity is unlikely the case for TG6, or TG3 in DH, and hence the response is much more subdued (at least as reflected by the level of serum antibodies), perhaps also explaining the absence of the full-blown symptoms of enteropathy. It remains to be seen if an enhanced expression and activation of TG6 akin to the TG2 response in gut occurs at the site involved, i.e., within the cerebrospinal fluid in cases of gluten ataxia.

The presence of TG6 antibodies in a group of patients without the HLA-DQ2 or -DQ8 also suggests that production of such antibodies is not always strictly linked to the HLAs conferring risk for CD. Moreover, of interest is the fact that in the group of patients with neurological manifestations and no enteropathy who had either HLA-DQ2 or -DQ8, there was significant over-representation of DQ8 (29%) when compared with Group 1 (4%). This indicates that differences exist in the HLA profile that predisposes to TG6 as opposed to TG2-driven autoimmunity. It remains to be seen if DQ8 and possibly DQ1 prove to be important susceptibility HLAs for the NCGS neurology cohort.

To investigate any influence of the HLA type and the presence or absence of TG2 antibodies within the NCGS group (Group 2), we also analyzed the data by dividing Group 2 into those with and without HLA-DQ2 or -DQ8 (see Table 1) and those with and without positive TG2 antibodies (Figure 3). Neither of these two parameters substantially influenced the type and severity of the neurological manifestations.

The presence of TG6 antibodies in 38% of patients with newly diagnosed CD presenting with the classic gastrointestinal symptoms to a gastroenterologist may suggest that these patients are susceptible to future development of neurological dysfunction if they continue to consume gluten. This is also supported by the fact that patients with CD presenting with neurological problems are likely to be diagnosed with CD significantly later (mean age 52.6±15.3
years) when compared with those presenting with gastrointestinal symptoms (mean age 43.8±15 years). It could be argued that the presence of gastrointestinal symptoms offers a therapeutic advantage to these patients as it increases the likelihood of them being diagnosed and treated early, as opposed to the neurology patients who on average are diagnosed 10 years later.

As yet, it is unknown at what stage of the immunological response against gluten that TG autoantibodies (TG2, TG3, and TG6) are first produced and appear systemically in relation to the development of symptoms. Although inferable from various lines of evidence, it has not been directly demonstrated that the patients with neurological manifestations (particularly those with CNS involvement) have such antibodies in their cerebrospinal fluid, and whether these antibodies are produced locally or derived from the circulation. However, immunoglobulin deposits against TG6 can be found in the cerebellum of patients with GA and deposits against TG2 can be found in the brain vessel wall in patients with GA (12,22).

Further evidence in support of a role for TG antibodies in disease pathogenesis comes from mouse models. TG antibodies (TG2 and TG6) cause ataxia-like deficits following intraventricular injection (23). Antibodies forming the characteristic deposits in the papillary dermis in DH are derived from the circulation, indicating that extraintestinal manifestations of GRD are antibody mediated (24). Furthermore, HLA-DQ8 transgenic mice develop some features of gluten sensitivity analogous to NCGS that are gluten dependent.

An important finding in this study is that patients with NCGS can present with neurological dysfunction in an identical manner to those patients with CD, suggesting similar immunological processes being responsible at least for the neural damage. This is also supported by the similar prevalence of TG6 antibodies in the two groups.

All the neurology patients described in this report were selected on the basis of positive antigliadin antibodies. Unfortunately, this serological test is no longer in general use as immunity laboratories are preferentially using newer assays (e.g., deamidated gliadin, endomysium, and TG2 antibody assays). These newer assays are far superior for diagnosing CD as they are based on specific molecular events occurring in CD pathogenesis, but unfortunately such assays are of limited use in the diagnosis of patients without enteropathy (Group 2) where molecular preferences show a bias that is distinct. Hence, in cases without enteropathy, the less selective marker AGA can provide an indication that further investigation is warranted, although not diagnostic by itself. In our experience, patients with NCGS are equally likely to respond to a strict GFD as are those patients with CD and neurological manifestations. Although TG6 antibody testing appears to be more specific for the neurological manifestations even in the absence of enteropathy, it is not as yet readily available. Currently, the best approach would be to include all serological testing (TG2, TG6, anti-endomysium antibodies, AGA) for patients suspected of having GRD.

Increasing recognition of the whole spectrum of GRD is the only way of improving diagnosis and thus avoiding the common problem of patients with neurological manifestations remaining untreated if duodenal biopsy does not reveal an enteropathy.

CONFLICT OF INTEREST
Guarantor of the article: Marios Hadjivassiliou, MD.
Specific author contributions: Marios Hadjivassiliou, Richard A. Grünewald, and David S. Sanders collected the data over the past 20 years. Marios Hadjivassiliou analyzed the data and produced the first draft. Dasappaiah G. Rao and Ptolemaios G. Sarrigiannis reviewed the neurophysiological assessments. Nigel Hoggard reviewed all the brain imaging. Peter D. Mooney and David S. Sanders performed all the gastroscopies and biopsies. Daniel P. Aeschlimann and Pascale Aeschlimann performed all the TG6 assays. Richard A. Grünewald was responsible for all the statistical analysis. All authors read and critically revised the manuscript and approved the final version.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE
✓ NCGS refers to patients with sensitivity to gluten in the absence of an enteropathy.
✓ There is no reliable serological marker for this entity.
✓ Not much is known of any neurological manifestations and any differences from patients with CD.
✓ The pathophysiology remains elusive.

WHAT IS NEW HERE
✓ Patients with NCGS develop neurological manifestations.
✓ Such neurological manifestations are similar to what is seen in patients with CD.
✓ Such patients may benefit from a GFD.

REFERENCES


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