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## Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity

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### Abstract

Celiac Disease (CD) is an immune-mediated disease dependent on gluten (a protein present in wheat, rye or barley) that occurs in about 1% of the population and is generally characterized by gastrointestinal complaints. More recently the understanding and knowledge of gluten sensitivity (GS), has emerged as an illness distinct from celiac disease with an estimated prevalence 6 times that of CD. Gluten sensitive people do not have villous atrophy or antibodies that are present in celiac disease, but rather they can test positive for antibodies to gliadin. Both CD and GS may present with a variety of neurologic and psychiatric co-morbidities, however, extraintestinal symptoms may be the prime presentation in those with GS. However, gluten sensitivity remains undertreated and underrecognized as a contributing factor to psychiatric and neurologic manifestations. This review focuses on neurologic and psychiatric manifestations implicated with gluten sensitivity, reviews the emergence of gluten sensitivity distinct from celiac disease, and summarizes the potential mechanisms related to this immune reaction.

### Keywords

Gluten; Schizophrenia; Neurologic; Immune; Celiac; Psychiatric

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## Introduction

Celiac disease (CD) is an illness which is currently well understood. This illness is caused by an immune reaction to gluten, a protein found in wheat, barley and rye, and is generally characterized by villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. Presenting symptoms typically include postprandial bloating, steatorrhea, and weight loss, and it is present in about one percent of the population [1]. The diagnosis is confirmed by testing for a number of different antibodies including anti-endomysial antibodies (EMA), anti-tissue transglutaminase antibodies (tTG), and anti-gliadin antibodies (AGA). In addition to understanding the cause of the disorder and the diagnostic tests to confirm it, we also understand the pathogenic mechanism related to intestinal damage [2] and the genetic basis of the disorder which includes haplotypes HLA-DQ2 or HLA DQ8. The increasing knowledge and understanding of this disorder has brought significant attention by physicians and health care workers in recent years as a disease with significant undesirable consequences. Yet, it is believed that many cases continue to go unidentified and untreated.

Only in recent years have we begun to understand gluten sensitivity, a gluten-mediated immune reaction that exists separate from CD and gluten allergic reactions (IgE mediated). Gluten sensitivity is estimated to occur at 6 times greater frequency than CD and is believed to be characterized by a different type of immune mediated reaction [3]. People with GS do not have villous atrophy or antibodies to tTG or EMA, but rather they can test positive to antibodies to gliadin [4]. Also, while the majority of people with CD test positive to HLA-DQ2 or DQ8, only 50% of people thought to be gluten sensitive will test positive for these haplotypes [2]. Another differentiating factor is the presence of interleukin 17A (IL-17A) gene expression in biopsy specimens of CD which is not present in gluten sensitive patients. In addition to laboratory evidence of this distinct difference [5], clinical data also provides evidence. Kaukinen et al. [6] had shown that in a population of slightly under 100 people who reported abdominal symptoms after consumption of gluten only 9% had CD, 8% had latent CD, 20% had a cereal allergy and 63% were not classified as having CD or an allergy. Of these 59 people, 10 (17%) presented with increases in CD3 T-helper cell receptor bearing intraepithelial lymphocytes but were negative for HLA DQ8. Forty percent also had anti-gliadin antibodies (either IgG or IgA). Lastly, Sapone and colleagues [5] recently reported that gluten sensitive patients in comparison to CD patients, showed normal intestinal permeability and activation of the innate but not the adaptive immune response. This suggests that in gluten sensitive patients there is a lack of adaptive immune response that prevents the autoimmune gastrointestinal insults that are seen in CD patients.

The relationship of celiac disease to neurologic and psychiatric complications has been observed for over 40 years [7, 8]. Gluten sensitive patients also have a host of neurologic and psychiatric complications. However it is notable, based on the lack of gut involvement, that neurologic and psychiatric complications seen in gluten sensitive patients may be the prime presentation in patients suffering from this disease. Therefore gluten sensitivity may easily go unrecognized and untreated. Data suggests that up to 22% of patients with CD develop neurologic or psychiatric dysfunction [9], and as many as 57% of people with neurological dysfunction of unknown origin test positive for anti-gliadin antibodies [10]. Neurologic and psychiatric complications observed with gluten-mediated immune responses include a variety of disorders. For example, a PubMed literature search (dates 1953–2011) located 162 original articles associating psychiatric and neurologic complications to celiac disease or gluten sensitivity. Thirty-six articles were located for seizure disorders, 20 articles for ataxia and cerebellar degeneration, 26 for neuropathy, 20 for schizophrenia, 14 for depression, 12 for migraine, and up to 10 articles each for anxiety disorders, attention deficit and hyperactivity disorder, autism, multiple sclerosis, myasthenia gravis, myopathy, and white matter lesions. Because the vast majority of research to date has not separated gluten

sensitivity from celiac disease the true prevalence of neurologic and psychiatric complications associated with each is difficult to quantify. This review however brings focus to the fact that gluten sensitivity is distinct from CD and that gluten-mediated immune responses may be the cause of patients presenting with a host of psychiatric and neurologic complications. We review here the literature as it relates to psychiatric and neurologic complications known to be associated with any gluten-mediated disorder (GS or CD) and the potential pathophysiology associated with these complications as seen in gluten sensitivity in particular.

## Evidence of Neurologic Complications

### Gluten Ataxia

The best-characterized neurologic complication related to gluten sensitivity is ataxia, now termed “gluten ataxia”. Gluten ataxia is characterized by positive anti-gliadin antibodies, changes in the cerebellum, and ataxic symptoms including upper or lower limb ataxia, gait ataxia, and dysarthria [11]. One study showed that 41% of 143 patients with sporadic idiopathic ataxia had anti-gliadin antibodies compared to only 12% of control subjects [10]. In addition to anti-gliadin antibodies, patients with gluten ataxia have oligoclonal bands in their cerebrospinal fluid, inflammation at the cerebellum, and anti-Purkinje cell antibodies [4]. Changes in the cerebellum on post-mortem examination include Purkinje cell loss with cerebellar atrophy and Bergmann astrocytosis [12]. Some persons with gluten ataxia have antibodies that show reactivity with deep cerebellar nuclei brainstem and cortical neurons. These studies also suggest that persons with gluten ataxia may have additional antibodies that react with Purkinje cells and are not present in patients with anything other than gluten ataxia alone. It seems likely that the Purkinje cells of the cerebellum share epitopes with gliadin proteins [13].

A study by Hadjivassiliou et al. [14] measured the response of patients with gluten ataxia and neuropathy to administration of a gluten-free diet. After 1 year on a gluten-free diet, the patients experienced significant relief of their ataxic symptoms on all tests. Several studies have shown that screening for celiac disease and gluten sensitivity is beneficial in patients with ataxias and neuropathies of indefinite origin [14–16].

### Epilepsy and Seizure Disorders

Epilepsy is another documented neurological manifestation of GS or CD. The prevalence of celiac cases in people with epilepsy ranges from approximately 0.8–6% [17, 18]. The clinical picture generally includes a specific triad of symptoms- occipital calcifications, seizures originating from a number of brain locations, and GS or CD. A study by Pfaender et al. [19] describes patients with visual manifestations due to seizure activity, which included blurred vision and seeing colored dots. In this study all the patients had bilateral cortical calcification and celiac disease. Researchers in Argentina identified 32 patients at their clinic with this triad of symptoms (seizures, CD, bilateral cortical calcification). Of the patients with hypodense areas in the white matter around their calcifications, three patients had a reduction of these areas on a gluten-free diet. As expected, seizure activity was better managed in the patients who received the earliest gluten-free diets [20]. A smaller study of four patients with this triad of symptoms reported that three of the four patients had significant reduction of their seizure activity after going on a gluten-free diet [21]. A number of studies have reported similar improvement in patients with this triad of symptoms encompassing seizures, GS or CD, and cortical calcifications [22–24].

Epilepsy related to GS and CD may not always manifest in the occipital lobe. For example, Peltola et al. [25] compared patients with temporal lobe epilepsy and hippo-campal sclerosis, to those with temporal lobe epilepsy and no hippocampal sclerosis, and to those

with extra-temporal epilepsy alone for prevalence of gluten sensitivity or CD. Seven of the 16 patients with temporal lobe epilepsy and hippocampal sclerosis were positive for GS while none of the patients from the other two groups had CD or GS. Overall, review of these epilepsy articles supports screening patients with idiopathic epilepsies for gluten sensitivity and celiac disease.

### **Other Neurological Manifestations**

Other neurological manifestations of gluten sensitivity and celiac disease include peripheral neuropathy [26], inflammatory myopathies [27], myelopathies [3], headache [28], and gluten encephalopathy [29]. White matter abnormalities associated with gluten sensitivity have also been reported [30].

### **Evidence of Psychiatric Complications**

A wide range of psychiatric symptoms and disorders have been associated with CD and GS. Those occurring mostly commonly, as reported here, include anxiety disorders [31] depressive and mood disorders [32, 33], attention deficit hyperactivity disorder (ADHD) [34], autism spectrum disorders [35], and schizophrenia [7, 36–38]. While there is limited research on the relationship of most psychiatric disorders to GS and CD, accumulating evidence suggests a variety of connections.

#### **Anxiety Disorders**

Various types of anxiety are associated with gluten intolerance. One study found that CD patients were significantly more likely to have state anxiety when compared to controls, and that after 1 year on a gluten-free diet, there was a significant improvement in state anxiety symptoms [31]. Other anxiety disorders such as social phobia and panic disorder have been linked to gluten response. Addolorato and colleagues [39] reported that a significantly higher proportion of CD patients had social phobia compared to normal controls. Additionally, a higher lifetime prevalence of panic disorder has been found in CD patients [33] and new studies have confirmed the increased association between CD and anxiety [40].

#### **Depression and Mood Disorders**

Depression and related mood disorders are reported to be associated with gluten sensitivity and celiac disease. One study found that major depressive disorder, dysthymic disorder, and adjustment disorders were more common in a group of CD patients compared to controls [33]. Increased prevalence of dysthymia in CD compared to controls was supported by a subsequent study [32]. Another study found that CD patients were more likely to be diagnosed with subsequent depression, but not bipolar disorder as compared to people without CD [41]. Ruuskanen et al. [42] found that an elderly population with gluten sensitivity was more than twice as likely to have depression when compared to the elderly sample without GS. Corvaglia et al. [43] have described improvement in depressive symptoms following a gluten-free diet.

#### **Attention Deficit-Hyperactivity Disorder (ADHD)**

A few studies have suggested that Attention Deficit Hyperactivity Disorder (ADHD) may be associated with gluten intolerance as well. A study measured ADHD symptoms in CD patients and found that these symptoms are “overrepresented” as compared to the general population. A 6-month gluten-free diet was reported to improved ADHD symptoms and the majority of patients (74%) in this report wanted to continue the gluten-free diet due to significant relief of their symptoms [34].

## Autism Spectrum Disorders

Autism spectrum disorders (ASD) have been associated with gluten intolerance in a number of studies. Association studies have shown the relationship between ASD and autoimmune disease, specifically CD. One study found an increased risk of ASDs in children with a maternal history of rheumatoid arthritis and celiac disease [44]. Another study of children with ASDs showed an increased family of disease, rheumatoid arthritis, and irritable bowel syndrome [45]. When compared to controls, persons with ASDs and their family members have been found to have a high percentage of people with abnormal intestinal permeability. Patients with ASD who have been treated with gluten- and casein-free diet have been found to have better intestinal permeability when compared to patients on an unrestricted diet [46]. Other studies have also shown that gluten- and casein-free diets are beneficial in ASD subjects [47–49]. Another study found that certain autistic patients produce antibodies against both Purkinje cells and gliadin peptides [50]. These interactions may be associated with the development of or exacerbation of ASD symptoms. It is worth noting that most research in this area involves gluten- and casein-free diets, making it difficult to discern whether or not the removal of casein may have additional beneficial effects.

## Schizophrenia

Schizophrenia may be the psychiatric disorder with the most robust relationship [51]. As early as 1953, Bender noted that children with schizophrenia were prone to having celiac disease. In 1961, researchers wrote a case study on five patients with schizophrenia and history of celiac disease who were admitted to the same hospital in the course of a year [52]. Dohan also published a number of schizophrenia and gluten studies. The first of these studies was published in 1966 and showed that the prevalence of schizophrenia was lower in areas of lower grain consumption. He also showed that a milk- and cereal-free diet improved schizophrenic symptoms, and the patients on this diet were moved to a non-locked ward more quickly than those with gluten added to their diet [53]. A similar study showed that these patients were discharged twice as quickly as those not on the diet [54] and a third showed that recovery is disturbed when gluten is added to a previously gluten-free diet [55]. Another article by Dohan et al. [56] involved intracerebral injection of rats with fractions of gliadin polypeptides. After high dose injections, reactions such as seizures, perseverative behaviors, and other unusual behaviors were noted. The authors suggest that this may be related to the pathogenesis of schizophrenia.

In 1997, a case study was published that described a woman with symptoms of schizophrenia who was diagnosed with CD following admission for her psychiatric symptoms. She presented with symptoms such as hallucinations, avolition, and telepathic thought. She showed slow fronto-temporal abnormalities on EEG as well as hypoperfusion in the left frontal cortex on SPECT scan. A gluten-free diet was administered and she showed remarkable improvement at follow-up. After just 6 months on the gluten-free diet, she no longer had hypoperfusion on SPECT scan and her psychiatric symptoms disappeared. She was even able to discontinue the use of antipsychotics and she remained symptom-free at a 1 year follow-up [36]. In a trial by Singh and Kay [55], 14 subjects on a locked research ward were put on a gluten-free diet followed by a gluten-challenge. Significant improvement by blinded assessors was reported on 30 of the 39 measures of psychopathology and social avoidance and participation. Rice et al. [57] reported changes on the Brief Psychiatric Rating Scale (BPRS) during a blinded study: out of a sample of 16 people with chronic schizophrenia, two improved in their levels of functioning in the gluten-free phase and one of those two demonstrated severe regression in the subsequent gluten-challenge [57]. A double-blind trial of 24 patients by Vliissides et al. showed changes in five out of 12 measures in the Psychotic In-Patient Profile (PIP) scale [58]. Negative studies may not have included any patients with gluten sensitivity [59].

More recently our group published a study using blood samples from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. We reported that the age-adjusted prevalence (23.4%) of anti-gliadin antibodies in people with schizophrenia ( $N=1473$ ) was significantly higher than that observed in general population samples (2.9%) [60]. A supporting study found that people with schizophrenia with recent onset of symptoms had increased levels of IgA and IgG antibodies to gliadin compared to both controls and schizophrenics with multi-episodes that were not of recent onset. Interestingly, the patients with schizophrenia with recent-onset psychosis had higher levels of antibodies than the schizophrenia patients who were multi-episodic [61]. A third study [62] also replicated our finding and reported 27% of patients with schizophrenia having anti-gliadin antibodies compared to 18% controls. Reichelt and Landmark [63] reported 19% in the schizophrenia group and 0% in controls.

A study by Samaroo et al. tested schizophrenia patients and otherwise healthy CD patients for their immune response to celiac-associated biomarkers including HLA DQ2/ DQ8, anti-TG2 antibodies, and anti-deamidated gliadin antibodies. The schizophrenia patients showed very little correlation to these biomarkers suggesting that their GS is not autoimmune-driven as in CD, and instead follows some other pathway of reaction. This provides further support for the notion that GS is distinct from CD patients in their disease pathogenesis [37].

## Postulated Effects of Neurologic and Psychiatric Complications

### Anti-Gliadin Antibodies

Recent research on mice and the effect of different gluten-related antibodies has returned some notable results that may help clarify the role of neurologic manifestations and its relationship to anti gliadin antibodies. Sera from two CD patients with no neurological complications and one from a GA patient with no enteropathy were injected into the lateral ventricle of mice. The mice were tested on a rotarod to determine the effect of the antibodies on their equilibrium. The various samples had different antibodies including anti-gliadin antibodies, anti-TG type 2, and anti-neural antibodies. A mildly significant effect was seen in the mice that received the CD samples. However, the mice receiving the sera from the GA patient experienced a dramatic effect on their equilibrium. The GA sera expressed high reactivity with cytoplasmic proteins of neurons. This demonstrates the difference in neurological effects of sera from CD patients with no neuropathy and a patient with gluten ataxia and neuropathy [64].

There may be cross-reactivity between Purkinje cell epitopes and gluten peptides. However, in patients with GA, gluten peptides are not the only antibodies that react with Purkinje cell epitopes. Immunohistochemistry has shown that removal of anti-gliadin antibodies from sera of GA patients does not stop all reactivity at Purkinje cell epitopes. Gluten ataxia patients have been found to have circulating anti-Purkinje cell antibodies and there have been improvements seen with intravenous immunoglobulin therapy [65, 66]. However, there may be other unknown antigen or antigens involved in this process which would be useful in further distinguishing neurological from bowel manifestations [67].

Synapsin I is a neuronal phosphoprotein found in most neurons of the central and peripheral nervous systems and plays a role in forming and sustaining the reserve pool of synaptic vesicles. Alaedini et al. [68], using ELISA, investigated the association between anti-gliadin antibodies and synapsin I. Research revealed that purified anti-gliadin antibodies had a strong immunoreaction to synapsin I using ELISA. Specifically, they found that patients' gliadin-specific IgG and IgA antibodies bound to synapsin I. In addition, they found that five out of nine patients with GS displayed either IgG or IgA antibodies to synapsin I, whereas no control subjects had a significant antibody reaction to synapsin I. The finding

that anti-gliadin antibodies may cross-react with synapsin I may provide insight into mechanisms mediating neurological dysfunction. In gluten sensitive patients, anti-gliadin antibodies could negatively affect synapsin I activity directly interfering with neurotransmitter release and possibly contributing to neurological impairments.

Previous studies have suggested that gliadin has the capacity to activate cytokine production in monocytes and macrophages [69]. In murine peritoneal macrophages treated with different concentrations of gliadin, there was a potent induction of pro-inflammatory genes, including TNF- $\alpha$ , IL-12, IL-15, IFN- $\beta$  iNOS, IP-10, and MCP-5, indicating that gliadin and its active peptides are capable of increasing expression of a repertoire of inflammatory genes [70]. Ashkenazi et al. showed that the response of lymphocytes to stimulation with subfractions of gluten was similar in a subgroup of schizophrenic patients to the response of lymphocytes from patients with CD [71–73].

### Other Potential Antibodies

Recently other antibodies have been linked to GS and neurological complications, including anti-GAD (glutamic acid decarboxylase) antibodies and anti-ganglioside antibodies. Glutamic acid decarboxylase is involved in the production of  $\gamma$ -aminobutyric acid (GABA), which is an important and widespread inhibitory neurotransmitter. At least 60% of patients with GA were found to have anti-GAD antibodies with high concentrations in the Purkinje cells and peripheral nerves [74]. This prevalence is as high as 96% for patients with both neurological problems and diagnosed CD. This may mean that in patients with enteropathy, these anti-GAD antibodies predispose them to developing neurological problems. GAD has a higher concentration in the Purkinje cells, peripheral nerves, in the enteric plexus. The presence of GAD in the enteric plexus may lead to the generation of these anti-GAD antibodies in patients with celiac and neurological problems [75].

Anti-ganglioside antibodies have been described in both neurological disorders and autoimmune diseases. Gangliosides are located on the surface of neurons and are involved in a number of functions on the cell's surface. Sixty-four percent of patients with CD and neurologic dysfunction tested positive for anti-ganglioside antibodies. Of patients with CD and no neurological problems, only thirty percent tested positive for these antibodies [76]. Several studies have shown that when anti-ganglioside antibodies bind to the nodes of Ranvier and myelin of peripheral nerves, they may cause demyelination and conduction block due to activation of lymphocytes [77, 78]. When placed on a gluten-free diet, the antibodies disappeared in about fifty percent of patients [76].

Recently tissue transglutaminase 6 (TG6) has been identified. It is similar to TG2, linked to CD, and TG3, linked to dermatitis herpetiformis [67], but is mostly expressed by a particular subset of neurons in the CNS. In one recent study 55% of patients with CD tested positive for more than one type of transglutaminase. In fact, 35% of these patients had antibodies that reacted to TG2, TG3, and TG6. In a comparison of patients with CD, GA with enteropathy, and GA without enteropathy, the GA group with enteropathy had the greatest prevalence of anti-TG6 antibodies and the patients with GA and no enteropathy had a significantly greater prevalence of these antibodies compared to the celiac group [67]. This research also showed that IgA and TG2 deposits accumulate in the muscular layer of brain blood vessels. This may allow the brain to be exposed to antibodies that could trigger an immune reaction. IgA deposits have also been shown to occur in the cerebellum, pons, and medulla [79].

### Serotonergic Effects

Gluten intolerance may also have some relationship to serotonergic functioning. One study found that a majority of adolescents with CD displayed depressive and behavioral symptoms

before the diagnosis of CD and had low free tryptophan levels. In that study, a gluten free diet was found to improve depressive symptoms and behavioral problems and increase free L-tryptophan levels to a level approaching significance [80]. After 1 year on a gluten free diet, patients with CD experienced a significant increase in major serotonin and dopamine metabolite concentrations [81]. Thus, this theory is incomplete but suggests that L-tryptophan and serotonin may be involved in the pathophysiologic link between gluten mediated immune responses and psychiatric comorbidities.

## Conclusions

Converging and accumulating evidence suggests that the gluten-mediated immune response is frequently associated with neurological and psychiatric manifestations, and GS represents a unique condition with a potentially different mechanism and different manifestations than celiac disease. More research is needed to help disentangle CD from GS and to understand the mechanisms of gluten-associated neurologic and psychiatric complications. These central nervous system effects of GS and CD are not trivial. Therefore, given the under-diagnosis and potential health consequences, this suggests the value of developing better ways of detecting and preventing the potential complications of these disorders.

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