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Autoantibodies related to ataxia and other CNS manifestations of gluten enteropathy

Gluten ataxia autoantibodies

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Abstract

Gluten ataxia and other central nervous system (CNS) disorders could be linked to gluten enteropathy and related autoantibodies. In this narrative review, we focus on the various neuro-logical manifestations in patients with gluten sensitivity/celiac disease, immunological and autoimmune mechanisms of ataxia in connection to gluten sensitivity and the autoantibodies that could be used as a biomarker for diagnosing and following. We focused on the anti-gliadin antibodies, antibodies to different isoforms of tissue transglutaminase (anti-TG2, 3, and 6 antibodies), anti-GlyR antibodies, anti-GAD antibodies, anti-DGP antibodies, *etc.* Most studies found a higher prevalence of these antibodies in patients with gluten sensitivity and neurological dysfunction, presented as different neurological disorders. We also discuss the role of a gluten-free diet on the clinical improvement of patients and also on imaging of these disorders.

Key Words: gluten ataxia; celiac disease; gluten enteropathy; autoantibodies; anti-gliadin antibodies; antibodies to tissue transglutaminase; anti-tTG antibodies; anti-TG6 antibodies; anti-GlyR antibodies; anti-GAD antibodies.

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Core Tip: Crucial insights into the complex nexus between gluten enteropathy and neurological disorders underscore the significance of specific autoantibodies. Anti-gliadin, anti-TG2, anti-GlyR, anti-GAD, and anti-DGP antibodies emerge as pivotal biomarkers, linking conditions from the gluten spectrum to diverse neurological manifestations. The prevalence of these antibodies in patients with gluten enteropathy and associated neurological dysfunction offers a diagnostic compass. Furthermore, the transformative impact of a gluten-free diet on clinical outcomes highlights its therapeutic relevance.

INTRODUCTION

Ataxia (from the Greek "lack of order") is a spectrum of neurological symptoms characterized by a dysfunction of motor control affecting coordination and balance, occasionally also accompanied by cognitive impairment. Depending on the affected area of the nervous system, ataxia could be divided into cerebellar, sensory or vestibular and, depending on the causative factor, into sporadic, hereditary and acquired ^[1].

Celiac disease (CD) is a chronic, multisystemic, autoimmune condition caused by gluten consumption in genetically susceptible individuals. Almost 20 years ago, Fasano *et al* reported that for every one patient with gluten enteropathy with gastrointestinal symptoms, there are seven patients with extraintestinal manifestations ^[2]. Moreover, it is assumed that the small bowel is no longer "the sole protagonist in gluten sensitivity" ^[3].

Conditions like dermatitis herpetiformis, gluten ataxia, *etc.*, changed our perspective on celiac disease. Although neurological disorders have been observed in patients with biopsy-proven celiac disease ^[4]. Hadjivassiliou *et al* demonstrated that gluten

sensitivity, and gluten enteropathy particularly, can manifest as neurological dysfunction alone [5]. The most prevalent neurological symptom of gluten enteropathy is ataxia (gluten ataxia) [6]. However, only a subset of individuals who present with neurological impairment due to gluten sensitivity will also have an enteropathy [7].

Additionally, idiopathic cerebellar ataxia (with a prevalence of 2-15%) [8], peripheral neuropathy (1.5-8%), some forms of epilepsy, migraine, attention/memory impairment, Guillain-Barre-like syndrome, chorea, myelopathy, mononeuritis multiplex, *etc.*, could be neurological manifestations of celiac disease [10].

The other individuals do not have histological signs of small intestinal damage but serological markers (serum autoantibodies) consistent with gluten enteropathy, a scenario similar to dermatitis herpetiformis. Genetic susceptibility may be tested in challenging cases because HLA DQ2 is prevalent in up to 90% of celiac disease patients [8].

IMMUNOLOGICAL AND AUTOIMMUNE MECHANISMS OF ATAXIA

The multisystem involvement in celiac disease is probably due to the expression of tissue transglutaminase (TG) isoforms, the main antigen for the disease, in many tissues and organs. The widespread localization of TG2 and TG3-6 includes skin, nervous system, pancreas, muscle, liver, joints, thyroid, *etc.*, allowing for multiple damage in case of anti-TG production [11]. However, the pathogenesis of neurological involvement in gluten enteropathy is unclear and still discussed. Previous hypotheses focused on intestinal malabsorption and related vitamin deficiencies (i.e., folic acid, cyanocobalamin, vitamin E, thiamine, *etc.*).

Pathologic studies on the CNS of patients with neurological CD, on the other hand, have recently revealed that immune-mediated processes can play a role by inducing neuronal damage and dysfunction [12]. In this vein, it has been revealed that circulating anti-neuronal antibodies (NA) of the IgG class target the central and enteric nervous systems (CNS and ENS, respectively) in a considerable number of neurological CD patients [13].

An important aspect of the different causes of ataxia is the possibility of autoimmune-mediated damage of the cerebellum or its related structures by impaired cellular or cell-mediated immunity or humoral immunity with production of antibodies targeting the neuronal structures [14]. Autoimmune neuronal damage could occur in the setting of classical autoimmune diseases presenting with ataxia when the cerebellum is one of the multiple autoimmune targets, such as in multiple sclerosis (MS), Behçet syndrome, connective tissue disorders such as systemic lupus erythematosus, hypothyroidism, *etc.* The term immune-mediated cerebellar ataxia (IMCA) is therefore used to describe primary or mainly pure cerebellar ataxia (CA) when the cerebellum is the main autoimmune target. IMCA is divided into two main subtypes – triggered by another disease or condition (neoplasm, infection, gluten enteropathy) and not triggered by another disease or condition (anti-GAD ataxia). When immune-mediated mechanisms are highly suspected but no serological markers are found, the disease is described as primary autoimmune cerebellar ataxia (PACA) [14-16].

Possible pathophysiological autoimmune-mediated mechanisms related to neuronal damage include both cell- and humoral-driven processes. Mechanisms such as deficits in immune tolerance or molecular mimicry have been linked to dysfunction of T- and B-cells and subsequent autoantibody production, cell cytotoxicity, exacerbation of local neural inflammation and cell death [1].

Studies in MS have shown that cell cytotoxicity has been linked to infiltration of CNS with Th1/Th17, CD8+ cells and macrophages and dysfunction of regulatory T cells resulting in increased production and secretion of cytokines leading to demyelination and cell death [17]. Cell-mediated cytotoxicity has also been suggested in some types of IMCA due to the increased CD8+ cells in the CSF and macrophage infiltrates in the neuronal structures [18].

An essential aspect of the pathophysiology of IMCA is the autoimmune response triggered by the formation of autoantibodies. The latter could be due to exposure to environmental factors or diseases and are directed against self-antigens, causing the formation of immune complexes, complement activation with subsequent cell

migration, tissue damage and organ failure. Autoantibodies in IMCA have been described against nuclear, intracellular and extracellular antigens and have also been found in the CSF, suggesting an increased permeability and disruption of the blood-brain barrier [19].

Depending on the different subtypes of the IMCA, the neuropathological findings could include loss of Purkinje neurons with Bergmann gliosis, gliosis of the cerebellar granular neurons, inferior olivary nucleus neurons and deep cerebellar nuclei, variable inflammatory changes and perivascular lymphoid infiltrates [20].

Some of the neurological manifestations in gluten enteropathy and the connection between gut and brain are shown in Figure 1.



Figure 1. Gut-brain interactions in health, pathophysiological mechanisms and clinical manifestations from nervous system related to gluten enteropathy. ⁴ Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (<https://creativecommons.org/licenses/by/3.0/>)

AUTOANTIBODIES IN GLUTEN ATAXIA AND OTHER CNS DISORDERS

ANTI-GLIADIN ANTIBODIES

Hadjivassiliou *et al* investigated the prevalence of gluten-related autoantibodies in a group of patients with gluten ataxia, hypothesizing that conditions related to gluten sensitivity and especially gluten enteropathy may explain a large number of patients with sporadic idiopathic and familial ataxia (including spinocerebellar ataxia, Friedrich's ataxia, sporadic olivopontocerebellar atrophy (OPCA) - a cerebellar variant of multiple system atrophy). The prevalence of antigliadin antibodies varied between 12-41% depending on the type of ataxia. Furthermore, gluten enteropathy was diagnosed in 24% of tested patients. The authors suggested that gluten ataxia could be the sole most common trigger for sporadic idiopathic ataxia [3,21].

Bushara *et al* also reviewed the presence of anti-gliadin antibodies in patients with gluten ataxia and other neurological manifestations in celiac disease patients. They gathered information on the prevalence of anti-gliadin antibodies varying from 1.9% to 16.7% depending on the ataxia type. In the case of ataxia of unknown cause, the prevalence of anti-gliadin antibodies could be up to 41% in different studies. However, the antibodies were significantly higher in people with ataxia than in the general population [8].

It is worth mentioning that anti-gliadin antibodies could present in up to 50% of patients with non-celiac gluten sensitivity. In line with this, some of the symptoms from the gluten enteropathy repertoire could also be attributed to neurological manifestations (i.e., brain fog, limb numbness, headache, depression). However, it is not known whether anti-gliadin or other celiac-related antibodies cause these symptoms [22,23].

ANTIBODIES AGAINST TISSUE TRANSGLUTAMINASE

Further investigations of the team were focused on the different isoforms of TG. The authors suggested that TG6 and anti-TG6 antibodies may activate the immune system in patients with celiac disease and neurological manifestations, such as idiopathic sporadic ataxia and peripheral neuropathy [24].

The authors reported that the prevalence of anti-tTG6 antibodies was 32% in idiopathic sporadic ataxia, 73% in gluten ataxia, 32% in celiac disease patients, and 5% in neurological controls, 4% in healthy controls. Interestingly, 42% of patients with gluten ataxia had enteropathy, and 51% of patients with ataxia had antibodies against TG6. Some patients were administered a gluten-free diet, and anti-tTG6 antibodies were significantly lowered or undetectable after 1 year of treatment [24].

Still, whether the anti-neuronal antibodies to CNS/ENS may target or cross-react with TG6 or other isoforms is unclear [10]. Other investigators connected anti-TG antibodies to neurological and enteral damage, not just an epiphenomenon [12,25].

Sarrigiannis *et al* hypothesized that brain hyperexcitability is a characteristic of patients with celiac disease and neurological symptoms (i.e., cortical myoclonus, ataxia, and other dysfunctions) [26]. Furthermore, it was evidenced that these patients tend to develop refractory celiac disease and are at risk of T cell lymphoma.

Recently, Ferlazzo *et al* published similar results on the significance of anti-TG6 antibodies in epilepsy, cerebral calcifications and gluten-related disorders. They confirmed that anti-TG6 antibodies are biomarkers for gluten-related ataxia and neuropathy but not epilepsy [27].

The prevalence of anti-TG6 antibodies was estimated as follows: 11% in patients with celiac disease, posterior cerebral calcifications and epilepsy; 22% - in patients with epilepsy and posterior cerebral calcifications but without celiac disease; 0% in patients with focal epilepsy of unknown origin; 13.6% - in healthy subjects [27].

Stenberg *et al* investigated celiac-related antibodies in children and adults with cerebral palsy, estimating a prevalence at about 36% for IgG anti-gliadin antibodies and 61% for IgA antigliadin antibodies, hypothesizing that poor growth in children with cerebral palsy could be associated with celiac disease. About 7% were positive for anti-tTG2 IgA and 17.5% - for anti-DGP antibodies [28,29].

When assessing the prevalence of anti-TG6 antibodies in patients with cerebral palsy, they found that 13% of patients with cerebral palsy and 6% of healthy controls were positive. Furthermore, the tetraplegic cerebral palsy subgroup had a significantly higher

level (35%) than other groups. Additionally, the authors concluded that an early brain insult and inflammation could be prone to autoimmunity development, especially associated with anti-TG antibodies [30].

Stamnaes *et al* speculate on the possible mechanisms of development and correlation between anti-TG6 antibodies and anti-TG2 IgA antibodies, which could explain the gluten enteropathy in patients with skin and CNS involvement [31].

We also know that TG6 expression is linked to neurogenesis in CNS in mice, with maturation and functional activity of the cerebellum and cerebral cortex [32].

It is now accepted that these antibodies are cross-reactive to different isoforms of TG, including TG2, TG3 and TG6. Furthermore, it was demonstrated that anti-TG antibodies from patients could induce ataxia-like defects in mice *via* intraventricular injection, revealing their pathogenetic potential [33]. The authors also reported the prevalence of anti-neural IgA/IgG antibodies in celiac disease patients without neurological manifestations at 75%.

Also, Wang *et al* and Li *et al* conducted genetic investigations identifying mutations in the TG gene associated with autosomal dominant spinocerebellar ataxia development, suggesting the broad role of TG6 in cerebellar functioning [34,35].

However, the specificity of anti-TG6 IgA antibodies to gluten ataxia could be questioned since such antibodies were also found in patients with amyotrophic lateral sclerosis (15.3% vs. 4.3% in healthy controls). Additionally, when tested for celiac-related HLA antigen alleles, 59.1% of seropositive patients were positive for celiac-related alleles. The authors concluded that amyotrophic lateral sclerosis could be associated with autoimmunity, gluten enteropathy, or sensitivity [36].

The most recent paper on anti-TG6 antibodies as a biomarker for gluten ataxia is by Sato et Nanri (2017). Their review followed the presence of anti-TG6 antibodies in sporadic ataxia and also shared an experience with patients with a profound sensory disturbance that contributes to ataxia in contrast to the usually reported mild sensory disturbances [37].

ANTI-NEURONAL ANTIBODIES

Caio *et al* investigated anti-neuronal antibodies in patients with celiac disease based on the data for neurological manifestations at about 10% in these patients [10]. They found anti-neuronal antibodies IgG to the central nervous system (CNS) (at titer 1:50 to 1:400) in 21% of patients. Moreover, the prevalence of these antibodies was higher in patients with neurological dysfunction (49% vs. 8%, $p < 0.0001$). Twenty-four percent of patients demonstrated anti-neuronal antibodies to the enteric nervous system (ENS), where 11/12 with antibody titer $> 1:200$ and severe constipation. Anti-neuronal antibodies to CNS and ENS were found in 7% and 5% of the healthy control group, respectively [10].

The authors conclude that anti-neuronal antibodies in patients with celiac disease could be used as a marker for neurological dysfunction. Besides, this study also provides supportive data on the immune-mediated pathogenesis of CNS and ENS impairment and gut dysfunction related to gluten enteropathy, thus recommending celiac-related antibodies screening for patients with gluten ataxia peripheral neuropathy drug-resistant epilepsy. Caio *et al* also discussed the role of anti-neuronal antibodies in damaging the morpho-functional integrity of the ENS, causing bowel dysmotility and altering secretion, which is linked to constipation [10]. Moreover, sera of patients with celiac disease containing anti-neuronal antibodies caused apoptosis and neuronal loss in neuronal cultures [12].

Similar to these results are those of Volta *et al*, who demonstrated that anti-neuronal antibodies are in low titers in patients with non-neurological celiac disease, strengthening the association between the presence of anti-neuronal antibodies to CNS and neurological involvement in celiac disease [13]. Hadjivassiliou *et al* also hypothesized possible mechanisms in the pathogenesis of neuronal damage in celiac disease patients (i.e., humoral and cellular immune infiltrate in CNS, mainly cerebellum) [6].

ANTIBODIES AGAINST GLYCINE RECEPTOR AND GAD

Other antibodies related to neurological dysfunction in celiac disease are those against glycine receptors. Kass-Iliyya *et al*, in their recent research (2021), discussed gluten enteropathy as a presentation of CNS hyperexcitability and cortical myoclonus, usually seen in refractory celiac disease. This CNS hyperexcitability could be attributed to glycine receptor antibodies (GlyR-Abs) or, more frequently, glutamine acid decarboxylase (GAD) antibodies [38].

The authors previously documented a connection between gluten enteropathy and anti-GAD-associated ataxia, improved with a gluten-free diet. They were interspersed with finding a similar association with anti-GlyR antibodies. Usually, anti-GAD antibodies are associated with Stiff person syndrome, a rare autoimmune condition characterized by neuropsychiatric symptoms and axial muscle stiffness and spasms [39-41].

Furthermore, a gluten-free diet can lower the levels of anti-GAD antibodies and clinical improvement. This raised the hypothesis that gluten sensitivity is broad spectrum of conditions where anti-GAD-related neurological manifestations could occur [26,42].

Kass-Iliyya also confirms that in the case of gluten sensitivity without enteropathy but with neurological involvement, antibodies against gliadin and TG6 could be the only positive biomarkers [38]. In line with this, Manto *et al* demonstrated with *in vivo* studies that anti-GAD antibodies inhibit GABA release leading to cerebellar ataxia [42]. Besides, antibodies to glycine receptors alter glycinergic neurotransmission *in vitro* [43]. Furthermore, it was shown that anti-GlyR antibodies related to neurological disease are a spectrum [44], and approximately one-fourth of all patients with these antibodies have other autoimmune disorders [40]. However, whether the gluten-free diet would benefit these patients is still unknown. Other authors suggested that the presence of these antibodies is an epiphenomenon rather than a pathogenetic mechanism. The other option is these antibodies are pathogenic- and the trigger is gluten sensitivity. Ventura *et al* suggested that a gluten-free diet in patients with celiac disease protects against developing other autoimmune diseases in adulthood [38,45].

THE ROLE OF RADIOLOGY AND IMAGING IN ATAXIA

Ataxia is a clinical sign, not a specific disease, with diverse etiologies. Usually, imaging has a role in identifying cerebellar damage. Finding the exact site of the changes aids diagnosis—unilateral damage causes ipsilateral symptoms, while diffuse damage results in symmetrical ataxia. Limb ataxia is caused by lesions in the cerebellar hemispheres and impaired gait results from damage to the middle part of the cerebellum ^[45].

Ataxia can be congenital or acquired. Congenital ataxia is characterized by a smooth, chronic progression, while acquired ataxia has a more acute manifestation. Acquired ataxia can be caused by various inflammatory diseases such as cerebellitis or cerebellar abscess. Other causes of ataxia are systemic inflammatory diseases, vascular diseases such as ischemic or hemorrhagic infarction, or intoxication. Ataxia can also be caused by vitamin deficiency, various endocrinological diseases, paraneoplastic syndrome, neurodegenerative diseases and cerebellar tumors ^[45].

Diagnostic imaging plays a significant key role in the diagnosis of ataxia. Computed tomography (CT) and especially magnetic resonance imaging (MRI) are the methods of choice for detecting ischemic and hemorrhagic infarcts. The diffusion-weighted technique (DWI) detects ischemic infarction up to 5 min after its onset, making the method indispensable in this regard. CT also immediately detects the hemorrhagic infarction. CT and MRI are the gold standard in diagnosing various cerebellar tumors and other tumors in the posterior cranial fossa with different origins ^[46].

In addition to acquired ataxia, imaging methods also play a role in diagnosing the congenital form of the disease ^[47]. The most common finding is atrophy of the cerebellum, which can be global or more pronounced in the vermis region. MRI, particularly T2 and FLAIR sequences, is the preferred method for diagnosing cerebellar involvement. Characteristic findings are hyperintense lesions in the T2 sequence, most often in the deep cerebral white matter. Non-specific signs associated with ataxia are also the cortical atrophy of the cerebral hemispheres, expansion of the lateral ventricles, and the increased intensity of the frontal and parietal brain white matter. These changes

are found in FLAIR sequences. Sometimes, atrophy of the cerebellum is combined with atrophy of the brainstem, with characteristic smoothing of the pons [47].

Spinocerebellar ataxia is a heterogeneous group of congenital ataxias, with over 28 subtypes described. A characteristic finding of this type of ataxia is the **degeneration of the cerebellum and its tracts**, as well as **the brainstem, basal nuclei, cortex and peripheral** nerves. Unfortunately, these findings are non-specific and do not always correspond to the severity of the disease. A modern diagnostic method is magnetic resonance morphography, which currently gives promising results [48,49].

Diffusion Tensor Imaging (DTI) is an important sequence in detecting ataxia. A reduction in fractional anisotropy is most commonly found in the corticospinal and the pontine tract. In some cases, an increased mean diffusivity is also detected [50]. Magnetic Resonance Spectroscopy (MRS) is another modern sequence used in ataxia. The most indicative markers are total N-acetyl aspartate (NAA), **myoinositol (mI), glutamate/glutamine (Glx), and total creatine (Cr) in the cerebellar hemispheres and NAA, mI and Glx in the pons**. The most important change is the disturbance of the ratios between NAA and mI [51].

Gluten ataxia is relatively common in celiac disease and can be found in patients without gastrointestinal symptoms. It occurs in both children and adults; the disease is characterized by a cerebellar type of ataxia and sometimes by a sensory type. In gluten ataxia, imaging methods (CT and MRI) reveal cerebellar atrophy, which occurs gradually but can sometimes occur suddenly. Differential diagnosis includes spinocerebellar ataxia and multisystem atrophy cerebellar type (MSA-C). In both diseases, atrophy is present, but typical for MSA-C is the disproportionate atrophy of the cerebellum and the brainstem, as well as the presence of T2 hyperintense lesions (typically in the pontocerebellar tracts, pons and the middle cerebellar peduncles) [52,53].

LIMITATIONS OF THE SEROLOGICAL TESTS FOR GLUTEN ENTEROPATHY

Nevertheless, we have to acknowledge the limitations of the serological tests and relying to them for making the diagnosis of gluten enteropathy, and gluten ataxia as

well. Several studies confirmed that ³serologic tests, particularly the IgA EMA and the IgA tTGA, have become a relatively sensitive and specific way to initially detect celiac disease. Many studies demonstrate a specificity of IgA tTGA greater than 95% and a sensitivity in the range of 90% to 96% and ¹EMA has a slightly lower and variable sensitivity but an excellent specificity (99.6%). However, many individuals without celiac disease may express AGA IgG antibody (sensitivity of AGA IgA among adults ranges between 0.65 and 1.0 and the specificity between 0.71 and 0.97). In line with this, ¹AGA IgG is similar in sensitivity to the AGA IgA, but the specificity is much lower, approximately 0.5. ¹Because of the variable and generally inferior accuracy of the AGA, the use of AGA IgA and AGA IgG tests is no longer recommended for identifying individuals with celiac disease [54-57]. Nevertheless, false positive antigliadin antibody ¹tests have been recorded in individuals with a variety of other gastrointestinal disorders, including esophagitis, gastritis, gastroenteritis, inflammatory bowel disease, cystic fibrosis and cow's milk protein intolerance. Moreover, we have also bear in mind that ¹serologic tests may have false positive results (usually low antibody titers) in patients with other immune or inflammatory conditions such as many neurological disorders. For this reason and others, AGA Institute recommended testing for celiac disease in persons with peripheral neuropathy, cerebellar ataxia, and recurrent migraine, but ¹confirmation of the diagnosis of CD requires an intestinal biopsy in all cases [56].

CONCLUSION

Based on the data accumulated so far, we can conclude that many autoantibodies related to gluten enteropathy and other conditions could be assessed in patients with ataxia or other undiagnosed neurological disorders, revealing the involvement of immunological mechanisms associated with celiac disease. Some of these antibodies are anti-gliadin antibodies, antibodies to different isoforms of tissue transglutaminase (anti-TG2, 3, and especially anti-TG6 antibodies), anti-GlyR antibodies, anti-GAD antibodies, and anti-DGP antibodies. Some of these autoantibodies are pathogenic, others –

epiphenomena, and for others - there is not enough data to conclude. The opposite is also valid – it is recommended to manage strictly and follow-up patients with celiac disease for the development of neurological dysfunction and other extraintestinal complications.

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