

# Cerebellar Ataxia, Celiac Disease and Non-Celiac Gluten Sensitivity

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## Abstract

Cerebellar ataxia (CA) is one of the most frequent neurological manifestations related to celiac disease (CD). Celiac disease is found in patients with a percentage ranging from 1.9% to 16.7%. Gluten cerebellar ataxia is purely cerebellar and involves the entire cerebellum. The clinical signs of CA are gait ataxia, limb ataxia, dysarthria, pyramidal signs, altered eyes motions, and progressive impairment of stability, and erect position. The patients affected by Gluten CA show an immunological response against a primarily brain expressed TG, such as TG6. The prolonged gluten consumption in patients with gluten ataxia leads to a progressive loss of purkinje cells in the cerebellum. An early diagnosis of CA and gluten related disorders (GRD) increases the possibility to improve the neurological process. Non celiac gluten sensitivity (NCGS) is defined by clinical evidence of improvement of symptoms following the introduction of GFD in the absence of enteropathy. The increased recognition of the whole spectrum of Gluten related disorders (GRD) is the best way to improve the time of the diagnosis and to avoid patients with neurological manifestation remaining untreated if duodenal biopsy does not reveal an enteropathy. Cerebellar Ataxia is equally responsive to GFD in CD and NCGS patients.

**Keywords:** CA, CD, NCGS

## 1. Introduction

Cerebellar ataxia (CA) is one of the most frequent neurological manifestations related to celiac disease (CD) (1), and may be the only and initial clinical manifestation of this disease (2) without any association with gastrointestinal symptoms or malabsorption signs. At present, there is agreement that every patient affected by CA of undetermined nature should undergo a serological screening for CD (3). "Gluten Ataxia" may be considered the first term used to describe idiopathic cases of sporadic ataxia with positive anti-gliadin antibodies (4).

## 2. Prevalence

Cerebellar Ataxia is found in patients with a prevalence of 1.9% to 16.7% (5, 6). Hadjivassiliou et al. (7) reported a CD prevalence of 20% in all patients with ataxia and, more specifically, 25% in patients with sporadic ataxia and of 45% in patients with idiopathic sporadic ataxia. In the majority of studies investigating this association, blood anti gliadin antibodies (AGA) were present (8).

## 3. Clinical Manifestations

Gluten ataxia is purely cerebellar and involves the entire cerebellum (9). The clinical signs of CA are gait ataxia, limb ataxia, dysarthria, pyramidal signs, altered eyes motions, and progressive impairment of stability and erect position (10). Rarely, CA is associated with myoclonus, palatal tremor, chorea and opsoclonus (11). Only 10% of all patients with CA and CD display gastrointestinal symptoms (12); however, in some cases of CD CA is associated with neuropathies (1). After a brain magnetic resonance imaging (MRI), 60% of patients with ataxia were found to have cerebellar atrophy (8). The severity of CA is assessed at presentation with a simple clinical rating scale as: 1) mild, when the patient is able to walk unaided, 2) moderate, when the patient needs walking aids/support to be able to walk, and 3) Severe, when the patient is wheelchair bound (13).

## 4. Diagnosis

Ibara et al. (14) suggested that gluten ataxia may be diagnosed if the following conditions are present, positivity of IgA AGA and/or IgG AGA, presence of sporadic CA,

duodenal histology compatible with CD, clinical response to gluten free diet (GFD). Anti-transglutaminase antibodies (TGA) IgG, such as TG2 and TG6, are often evident in this group of patients and are correlated to an immune response in the central nervous system (CNS) (15). Antibodies to TG2 and TG6 may be present in patients with ataxia and blood negative AGA (7). Gluten ataxia has a late mean age of clinical presentation, on average 53 years (range 13 to 90) (7) with a diagnostic delay of 10 years when compared to patients presenting with gastro-intestinal symptoms (mean age 43.8 +/- 15 years) (15). Hadjivassiliou et al. (15) reported a prevalence of 78% of Blood IgG AGA, 65% IgA AGA, and 43% with both antibodies IgG and IgA. At present, however, the availability of TG6 antibodies analysis/testing is limited because these antibodies had only been discovered recently (2006) (15) and their importance in neurological manifestations of CD had not been established until 2008 (15). The role of autoimmunity in CD is well established due to the presence of a recognized target auto-antigen in the form of TG2 (13). The patients affected by gluten CA showed an immunological response against a primarily brain expressed TG, such as TG6 (16). Immunoglobulin deposits against TG6 and TG2 in the brain vessel walls could be found in patients with gluten ataxia (17). At this point, the time when Transglutaminase (TG) antibodies such as TG2, TG3, and TG6, appear in the blood stream, is not noted (15). Magnetic resonance (MR) spectroscopic studies may show evidence of abnormal cerebellar neuronal physiology (18). A significant difference in mean N-acetylaspartate/creatine levels has been observed between patients with gliadin antibodies and healthy controls (18).

## 5. Treatment

The prolonged gluten consumption in patients with gluten ataxia leads to a progressive loss of Purkinje cells in the cerebellum. Patients with celiac disease and CA have a blood deficit of vitamin E (19). However, the pathogenetic grounds of CA connected to CD are still unclear, and the role of gluten toxicity and blood vitamin E deficit need further studies (20). Only a small number of patients with CD and CA showed a clinical improvement after vitamin E therapy (21). Cerebellar ataxia may develop as paracerebellar syndrome and it could be the initial manifestation of a T cell intestinal lymphoma with the development of lymphomatous metastases in the cerebellum (21). Hadjivassiliou et al. (15) demonstrated that the benefit of the diet is independent from the presence of enteropathy. The loss of cerebellar purkinje cells may be irreversible and the duration of CA before the diagnosis may be considered a good predictor of response to GFD (9). An early diagnosis

of CA and gluten related disorders (GRD) increases the possibility to improve the neurological process (8); the clinical improvement is usually seen 1 year after starting the GFD (9) and continues for a period of about 2 years. The disappearance of serum antibodies to gluten are the best marker of the strict respect of the GFD, and a period of 6 to 12 months is generally needed to obtain the disappearance of serum antibodies (9). All patients showing sporadic unexplained sub-acute or chronic CA should be tested with the serological markers for gluten related disorders (9). It is important to underline that a strict GFD may reduce disability and partially arrest the disease's progression (9). Antibodies to TG6 are often associated with neurologic manifestations of CD, yet, these serological tests are not routinely available (10).

## 6. Cerebellar Ataxia in Non Celiac Gluten Sensitivity (NCGS)

Non celiac gluten sensitivity (NCGS) is defined by clinical evidence of improvement of symptoms, following the introduction of GFD in the absence of enteropathy (22). Autoantibodies, such as TG2, are absent in NCGS. The presence of Anti Gliadin Antibodies (AGA) and particularly IgG AGA may be an indicator of NCGS in more than 50% of patients that refer to the gastroenterologist (23). Hadjivassiliou et al. (15) reported on 114 patients with NCGS and gluten ataxia (GA), 68 of which had circulating TG6 antibodies. In the same study, the prevalence of TG6 antibodies in GA patients was similar in CD (67%) and NCGS (60%) patients. The authors also noted the presence of TG6 antibodies in a group of patients without HLA-DQ2 and DQ8, suggesting that the production of these antibodies may not be correlated with the human leukocyte antigen (HLA) haplotype present in patients with CD (15). The increased recognition of the whole spectrum of gluten related disorders (GRD) is the best way to improve the time of diagnosis and to avoid lack of treatment in patients with neurological manifestations if duodenal biopsy does not reveal an enteropathy (15).

## 7. Conclusions

The diagnosis of CA associated with CD or "Gluten Ataxia" should be confirmed only if a stabilization or an improvement of neurological symptoms is evident after the starting of a GFD (9). Loss of Purkinje cerebellar cells may become irreversible if the diagnostic delay of CD increases; the duration of CA before the diagnosis of CD may be considered a good predictor of response to GFD (9). Immunosuppressant therapy could be considered in selected cases

without response to GFD (24). Clinical improvement of CA in CD is evident after 12 months of GFD and clinical symptoms may still improve in the following 2 years (9). Furthermore, CA may be considered a potentially and reversible neurologic disorder and for this reason, all patient with CA should be screened for gluten related disorders (9). Cerebellar Ataxia is equally responsive to GFD in CD and NCGS patients (15).

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