

# Neurological Manifestations of Celiac Disease in Children and Adults

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## ABSTRACT

Celiac disease (CD) is a common, life-long, autoimmune condition, affecting the small intestine of genetically susceptible individuals. The classical clinical picture is disappearing as awareness progresses and the extra-intestinal presentation is emerging. Skin, endocrine, hepatic, skeletal, hematological, gynecological, infertility, dental, and behavioral abnormalities are emerging. Among the new growing domains is the extra-intestinal presentation of CD affecting the peripheral and central neurological systems. This review highlights neurological presentations in these patients, focusing on the clinical signs/symptoms in the pediatric and the adult age group, separately.

Keywords: Celiac disease, neurology, children, adults

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## INTRODUCTION

Celiac disease (CD) is a life-long autoimmune condition [1] of the gastrointestinal tract, affecting the small intestine of genetically susceptible individuals. Gluten, which is the storage protein of wheat and its alcohol-soluble gliadins, are the offending inducers of the disease together with structurally related molecules found in barley and rye. Nevertheless, additional environmental factors such as infections might play a role in CD induction [2]. Tissue transglutaminase (tTG) is the autoantigen against which the abnormal immune response is directed to [3] and two main auto antibodies: anti-endomysium and anti-tTG are the most useful serological markers to screen for the disease [4]. Recently, two additional autoantibodies, namely, anti-deaminated gliadin peptide and anti-neoepitope tTG were found to be reliable for CD screening [5]. HLA-DQ2 and HLA-DQ8 molecules are the most important, so far known, predisposing genetic factors. A lot is known on the pathogenesis of the disease. The sequential chain of events operating in the disease was recently unraveled, and gives the hope for future therapeutic strategies [6]. Furthermore, its epidemiology, prevalence and clinical presentation are changing constantly and with time; new clinical presentations are depicted and widen the plethora of clinical variability of CD [7].

It has been shown that the classical intestinal clinical picture is disappearing and the extra-intestinal presentation is emerging. Skin, endocrine, hepatic, skeletal, hematological, gynecological, infertility, dental, and behavioral abnormalities are often described (Table 1) [8]. With the growing awareness of family practitioners, hematologists and gastroenterologists, and now gynecologists and neurologists, the diagnosis of CD

is increasingly being made in adults. About 20% of the newly diagnosed cases occur in patients older than 60 years of age [9]. One of the growing domains is the extra-intestinal presentations of CD affecting the peripheral and central neurological systems [10–17]. Epilepsy, cerebellar ataxia, peripheral neuropathy, myoclonic ataxia, progressive leukoencephalopathy, cerebral vasculitis, dementia, migraine, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, and Guillian–Barre-like syndrome were described. More recently, a range of “soft” neurological disorders were found to be associated with CD. Chronic headaches, developmental delay, hypotonia, learning disorders, or attention-deficient/hyperactivity disorder appeared in the literature [10]. Parts of these presentations are age-dependent.

This review highlights those neurological pictures along the human life-span, focusing on the clinical signs/symptoms in the pediatric and the adult age group, separately.

## NEUROLOGICAL PRESENTATIONS OF ADULT CD

Hadjivassilou and coworkers made the intriguing observation that patients with a variety of cryptogenic neurological disorders including ataxia, neuropathy, myelopathy, and myopathy had high (57%) prevalence of anti-gliadin antibodies (AGA) [18]. Following their publication many studies were published on the association between CD and neurological complication.

Looking at it the other way around, neurological complications are reported in 8–10% of CD patients including peripheral

**Table 1.** The non neurological Extra-Intestinal manifestations of CD

Dermatitis Herpetiformis
Type 1 Diabetes Mellitus
Autoimmune Thyroiditis,
Iron Deficiency Anemia
Arthritis and Arthralgia
Chronic Hepatitis
Osteoporosis
Gynecological abnormalities
Infertility
Dental disease
Behavioral abnormalities

neuropathy, myelopathy, cerebellar ataxia, progressive multifocal leukoencephalopathy and epilepsy [19].

Regardless of the etiology, if not promptly treated, CD can cause irreversible neurological damage [19]. In support of this hypothesis, a significant correlation was found between the duration of the disease preceding diagnosis and treatment, and the neurological findings detected even years after the diagnosis [19].

Neurologic symptoms may be the first manifestation of silent CD. CD should therefore be considered in patients manifesting polyneuropathy, ataxia and memory disturbances of unknown etiology [20], or even with neuropsychiatric manifestations like depression, attention deficits, autism, and schizophrenia [21].

### Cerebellar Ataxia

Cooke and Smith [22] described a group of 16 patients with biopsy proven CD who had gait ataxia and peripheral neuropathy. They postulated that CD was the cause of these neurological abnormalities, as other etiologies were excluded. Thus, to date, patients with ataxia of unknown cause should be screened for CD [12].

The clinical presentation is indistinguishable from other forms of cerebellar ataxia, features including progressive unsteadiness of gait, and limbs [13]. The mean age at onset in their study was 53 years, with both sexes affected equally.

Gazed evoked nystagmus and other ocular signs of cerebellar dysfunction are found in up to 80% of cases [23].

Cerebellar atrophy may be detected by MRI in patients with gluten ataxia [13, 24], and post mortem findings demonstrate atrophy, gliosis, Purkinje cell depletion and degeneration of the posterior columns of the spinal cord [13, 22].

On average, AGA seem to be more prevalent in ataxia than in the general population (30% in ataxic patients compared with 8–12% in controls), suggesting an association between cerebellar degeneration and gluten sensitivity [12, 25]. AGA are found also in genetically determined ataxia and in Huntington's disease [23]. This finding should stimulate interest on the possible mechanism by which a genetically determined ataxia or other neurodegenerative process can result in the generation of antibodies against gluten.

The effect of gluten-free diet on ataxia varies [12]. There are few studies, mainly case reports, of the effect of gluten-free diet on the neurological manifestation of gluten sensitivity.

Immunomodulation with intravenous immunoglobulins has been reported to be beneficial [26] and thus could be considered if strict gluten-free diet has not resulted in any improvement of the ataxia within a year, or if the ataxia is rapidly progressive [23].

### Peripheral Neuropathy

Peripheral neuropathy is the second commonest neurologic manifestation of gluten sensitivity [27]. Evidence for peripheral neuropathy has been found in up to 49% of CD patients [12].

Chronic distal, symmetric, predominantly sensory neuropathy is described most commonly in patients with CD. Motor weakness is rare and confined to the ankles [12, 22]. Mononeuropathy multiplex is another presentation that was reported in patients with CD [28].

Electrodiagnostic studies in patients with a predominantly sensory neuropathy were normal, minimally abnormal, or have typically revealed only axonal changes [29]. Demyelinating changes have been rarely reported [30].

The effect of gluten-free diet on peripheral neuropathy and other neuromuscular disorders associated with CD is equivocal, and although autoimmune mechanisms are likely to be responsible for the peripheral neuropathy described with CD, there is minimal data regarding immunomodulatory treatment.

### Epilepsy

The prevalence of CD among epileptic patients has been reported to range from 1:40 to 1:127 [13]. High prevalence of epilepsy (3.5–5.5%) was reported in patients with CD compared with controls [31, 32]. Moreover, it has been suggested that gluten-free diet adhered shortly after the onset of epilepsy can control seizure occurrence and decrease antiepileptic medication but cannot cure the disease [33].

Visakorpi et al. [34] described a unique and rare syndrome of CD with bilateral occipital cerebral calcifications, occurring mainly in the parieto-occipital region and epilepsy.

### Headache

Gabrielli et al. reported an association between migraine and CD. CD was found in 4.4% of patients with migraine compared with 0.4% in controls [35]. Headache can be a symptom of CD in its classic, atypical, and silent form that responds to gluten-free diet [36]. Further studies are needed to assess this correlation.

### Autonomic Neuropathy

Patients with CD frequently present gastrointestinal abnormalities [37], some of which, like those in upper gut motility, may be related to dysfunction of autonomic nervous system (ANS) [38].

Usai et al. [38] has reported that abnormalities in the ANS were found in 45% of celiac patients affected by upper gastrointestinal symptoms. Moreover it was shown that ANS dysfunction was not affected/improved when patients were on proper gluten-free diet [37].

### Various Other Neurological Manifestations

Other neurological manifestations have been described in the form of case reports in adults with CD. These include chorea [39], cerebral vasculitis [40], Huntington's disease [41], neuromyotonia [42], and progressive leukoencephalopathy [43].

## NEUROLOGICAL MANIFESTATIONS IN CHILDREN

The number of publications of neurological manifestation in CD in childhood is far below those in adults, pointing to the fact that most probably it is an age-dependent phenomenon.

### Epilepsy

The increased prevalence of epilepsy among CD patients is known for more than three decades. Table 2 summarizes the major studies in the pediatric age group on the topic.

The conclusion that can be drawn from Table 2 is that the prevalence of epilepsy is extremely variable in children. About 0–10.7% of CD children exhibited convulsive disorders and 1.1–2.8% of the children with epilepsy had CD. Furthermore, brain imaging abnormalities range from 0% to 20% in CD patients and neurological disorders.

One of the well-characterized syndromes of epilepsy and CD was described in children by Gobbi et al. [44] It includes epilepsy, occipital calcifications, and CD. This manifestation rarely improves on gluten-free diet. However, some favorable outcome was described in childhood complicated epilepsy, even in Lennox–Gastaut variant [45, 46] Despite numerous recommendations in the literature to screen children with neurological problems for CD, or to screen pediatric population with CD for neurological disorders [10, 45–48], there is no consensus and there are contradictive opinions.

Recently, Ruggieri et al. [49] reported a low prevalence of neurologic and psychiatric manifestations in CD children. Only 4 epileptics were found among 835 children with CD and in 630 children with neurological disorders who were serologically screened for CD, 7 were found to have positive CD serology, 6 of whom had convulsions. In this “negative” study, the authors concluded that children with neurologic disorders did not exhibit a higher prevalence of CD.

### Peripheral Neuropathy

Peripheral neuropathy is less common than convulsive disorders in the pediatric CD population. Only 1 girl with acute demyelinating neuropathy was found among 835 CD children who were screened neurologically [49]. Two CD children developed a chronic axonal polyneuropathy that continued, with no improvement on gluten-free diet [50, 51]. Two of the 27 children with CD had peripheral polyneuropathy when screened neurologically [52]. The exact pathogenesis of this condition is unclear. There are conflicting reports about the relationship of the neuropathy with gluten or vitamin depletion.

## RARE ADDITIONAL NEUROLOGIC ABNORMALITIES IN CHILDREN WITH CD

### Headaches

About 24.8% of 88 CD children complained of headache. Interestingly, 77.3% of them responded to gluten-free diet. Of the 79 children with headache 5% were diagnosed with CD [52]. The increased incidence in headache led the authors to suggest headaches as a possible atypical presentation of CD in children. Other studies report the contrary, with only 0.35% of a large CD and neurologic population cohort suffering from headache [49].

### Mental Retardation, Bipolar Disorders, Myelopathy

Those were rarely described in the pediatric age group with CD [49, 52].

**Table 2.** Neurologic manifestation in children with CD

No	Brain imaging abnormality %	% of epileptic\CD	Population size of CD\epileptic	Reference
1	0	0	36 CD	17
2	20%	10.7 epileptic	75 CD	19
3	0	0.48 epileptic	835 CD	24
4	0.38	1.15 CD	783 epileptic	17
5	1.4	2.8 CD	72 epileptic	18
6	0	100 CD	1 epilepsy	21
7	0	100 CD	1 epilepsy	22
8	0	2 CD	255 epileptic	23
9	0.95	1.1 CD	630 neurologic/psychiatric disorders	24
10	–	1.4 CD	206 neurological disorders	25

## “Soft” Neurological Disorders (Hypotonia, Developmental Delay, Attention and Hyperactivity Disorders, and Tics)

Those were found to be more prevalent in pediatric CD (21.6%, 15.5%, 20.7%, 2.4%, respectively) versus general population (3.8%, 3.3%, 10.5%, respectively) [10]. However, a more recent survey disclosed a much lower prevalence, reaching the numbers in the general population [49].

## THE PATHOGENESIS OF NEUROLOGIC MANIFESTATION IN CD

Although a lot of progress was made in understanding the pathogenetic cascade of the intestinal injury in CD, the pathogenic pathways of the neurologic injury have yet to be elucidated. Several hypotheses are suggested [13, 14, 17] (Table 3):

1. Immune-driven mechanism by an autoantibody (anti-ganglioside or others).  
These autoantibodies can arise through molecular mimicry and antibody cross-reactivity to foreign or native components. Of note, AGA were found to react with human cerebellar tissue; anti-Purkinje cell antibodies cross-react with gliadin and gliadin can bind to GM1 ganglioside.  
There is indirect evidence of a pathogenic involvement of anti-ganglioside antibodies in autoimmune neuropathies [13]. CD is associated with other autoimmune disorders, partly to be due to a shared genetic mimicry (HLA alleles). This raises the question whether such a genetic tendency can explain the neurological complications associated with CD.
2. During the development of the intestinal injury in CD there are processing, degradation, deamination, and molecular changes resulting in the formation of new epitopes. Examples of such a process are two newly used serological markers: the anti-deaminated gliadin peptide and the anti-neo-epitope of the tTG [5]. Deaminated gliadin peptide forms epitopes that transglutaminase antibodies recognize. The neo-epitope formation can induce numerous autoantibodies that can impact intestinal, extra-intestinal, and neurologic components.
3. The major auto-antigen in CD is the tTG. Its specific autoantibody is actively involved in CD genesis. Deposits of this antibody were detected in extra-intestinal locations including around brain vessels wall, mainly in the cerebellum, pons, and medulla.
4. Re-circulation of committed T cells into the human CSF may further enhance gut-primed gliadin-reactive CD4<sup>+</sup> T

cells. These cells interact with specific B cells resulting in a plethora of local pathogenic autoantibodies.

5. The presence of neuropathy in patients on gluten-free diet has also been reported [53], suggesting direct neurotoxic effect of gluten, and may point to different mechanisms.
6. Diseases associated with CD or dietary deficiencies: Careful investigation must be carried in order to rule out other etiologies for CD neuropathy including diabetes that is associated with CD and may cause small fiber neuropathy, as well as nutritional causes. Folate or vitamins E, B12, B6, and B1 levels should be measured to rule out those deficiencies. Replacement vitamin therapy, however, does not resolve neurologic clinical symptoms in the majority of cases [21]. Moreover, most neurological patients with CD do not show evidence for any nutritional deficiencies [21].

## Why CD Children are Protected from Neurological Complications

Adults with CD are at higher risk of developing neurological and/or psychiatric disturbances compared with children (26% vs 2.6%) [49]. It is also correct on the opposite direction. More adults with neurological/psychiatric presentation are prone to have CD than pediatric patients. Furthermore, many neurological manifestations in the adult CD population are very rarely, if at all, reported in children, cerebellar ataxia being an example.

Several mechanisms can explain the above discrepancy:

Children with CD are protected against central or peripheral neurological complications by the following ways:

1. Shorter duration of CD. There is a possibility that the developing nervous system is protected against offending agents or the neuronal apparatus needs time to be irreversibly damaged.
2. CD is more symptomatic in the pediatric age group, resulting in earlier dietary therapy.
3. Children adhere to gluten-free diet more than adolescents and adults. Compliance to dietary restrictions may protect them from neurological injury.
4. The pathogenic antibodies (anti-gliadin, anti-tTG, or others) need time to penetrate the nervous system and produce permanent damage.
5. If the neurological complications are mainly of an autoimmune mechanism, it is well established that the autoimmune processes and diseases are age dependent.

In summary, neurological manifestations, such as ataxia, epilepsy, and peripheral neuropathy, are increasingly known to be the presenting features of CD. Thus screening for CD should be recommended in many neurological disorders especially when the etiology is not obvious. The prevalence of neurological manifestations in CD is striking, and thus the patient's symptoms must be investigated carefully. The mechanisms underlying the nervous system involvement in CD are not completely identified.

Obviously, the patients' gluten-free diet had resolved intestinal symptoms, but had not always cured the neurological

**Table 3.** Hypothesis of the pathogeneses of the neurological manifestations in CD

Humoral Immune Mechanism
Antibodies to Gliadin
IgG Antibodies to Gangliosides
Vitamin Deficiencies
Direct neurotoxic effect of gluten

manifestations and had not prevented the development of neurological deficit.

Thus further studies are required to assess the effect of gluten-free diet and immunomodulation on these disorders and to investigate the underlying mechanisms of nervous system involvement associated with gluten sensitivity.

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