REVIEW ARTICLE

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# Neurological Manifestations of Celiac Disease

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**Abstract**

Celiac disease (CD) is a rare malabsorption syndrome mainly occurring in childhood which is now recognized as the most common food intolerance disease in the world. CD is associated with a wide spectrum of extra intestinal manifestations. Neurological involvements of CD were first attributed to malabsorption due to changes in the mucosal architecture of the small intestine. Neurological manifestations were more frequent in middle-aged adults, but were rare in children. The most common central nervous system manifestations include cerebellar malfunctions, seizures, dementia, multiple sclerosis like presentations, motor neuron diseases, headaches, movement disorders, and neuro-psychiatric presentations. On the other hand, the peripheral nervous system involvement includes different types of peripheral neuropathies and muscular involvements. In this study, we embarked on a short review to go through the neurological presentations and problems of CD.**[GMJ. 2013;2(2):60-75]**

**Keywords:** Celiac Disease; Nervous system; malabsorption syndrome; Review



## Introduction

Celiac Disease (CD, also called non tropical sprue or gluten-sensitive enteropathy), an autoimmune enteropathy, was first described in 1888 by Samuel and was originally considered a rare malabsorption syndrome mainly occurring in childhood which is now recognized as the most common food intolerance disease in the world. CD is triggered by ingestion of wheat gluten and the related cereal proteins and may arise at any age with a growing proportion of new cases diagnosed in adults, especially in genetically predisposed individuals [1-3]. Recent studies have revealed that CD affects approximately 1% of the general population across the globe [4]. Almost all the CD patients have a genetic susceptibility characterized by HLA-DQ2 and/or HLADQ8 positivity. Genome-wide association studies during the last 3 years have reported more than a dozen new susceptibility loci for CD [1]. Analysis of eQTL data from these and previously established risk loci sheds light on the genetic pathways underlying this common autoimmune disease [5].
CD diagnosis requires the positivity of transglutaminase antibody and MARSH III grading at histology. It is still debated that MARSH I or II are overt in CD even in association with

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positive antibodies. Gluten hypersensitivity requires the positivity of transglutaminase antibody with normal histology or MARSH I and II grading at histology [6]. Small-bowel mucosal morphology was classified according to the Marsh criteria: normal histology (Marsh 0), infiltrative lesion (Marsh I), infiltrative-crypthyperplastic lesions (Marsh II), partial villous atrophy (Marsh IIIA), and subtotal villous atrophy crypt hyperplasia (Marsh IIIB)[7,8].

CD is associated with a wide spectrum of extra intestinal manifestations [9]. Although CD is one of the most common lifelong inflammatory diseases, most affected individuals remain undiagnosed [1]. The patients with asymptomatic CD who have no symptoms and respond to gluten withdrawal are often diagnosed through screening programs or in case-detecting strategies for the patients with disorders that are accompanied with a high risk for CD [10,11]. Among the affected subjects, only 25% developed the clinical symptoms. Many patients, especially those presenting in adulthood, have minimal or atypical symptoms, unexpected associations such as epilepsy, and various undefined neurological disorders [2,9]. Gluten intolerance is also another synonym used for CD to indicate the clinical improvement of the patients subsequent to Gluten Free Diet (GFD) initiation, even when they do not have CD [12-14].

Neurological manifestations of CD have been investigated and reported in a number of studies by many researchers. However, there are a few review studies regarding this aspect of CD presentations. In the present study we aimed to provide a narrative review on the neurological presentations of CD.

## History and Demography

Carnegie Brown in 1908 reported the first neurological manifestations of CD in two patients with "peripheral neuritis" [15]. Besides, Elders reported the association between "sprue" and ataxia in 1925 [16]. In 1966, Cook and Smith described 16 patients with different neurological manifestations associated with adult CD, including severe progressive neuropathy, gait ataxia, and limb ataxia. They also reported the first postmortem neuropathological examinations of the patients with neurological involvement of CD showing extensive perivascular inflammatory changes in both central and peripheral nervous systems. A striking feature was the loss of Purkinje cells with atrophy and gliosis of the cerebellum [17]. Neurological involvements of CD were first attributed to malabsorption due to changes in the mucosal architecture of the small intestine[18]. Malabsorption theory has been outmoded as overt malabsorption in CD is rare due to developed diagnostic methods. Studies demonstrated the presence of neurological complications of CD in spite of normal amounts of essential nutritional elements. In 1966, Marks et al. suggested a probable association between inflammatory mechanisms and CD by demonstrating the similar pattern of enteropathy in both dermatitis herpetiformis, as an inflammatory disease, and CD [19]. On the other hand, Willis et al. also took detailed histories and performed careful clinical examinations in 35 patients with dermatitis herpetiformis and found no evidence for immune mediated neurological damage [20]. Presence of inflammatory cell infiltration in the histopathological findings of the patients with CD and neurological manifestations led the investigators to think of an autoimmune mechanism [17,21].

## Prevalence

Table 1 shows retro/prospective series of the CD patients investigated for neurological manifestations. Overall, 334 out of the 1562 patients with CD had neurological manifes-

**Table – 1.** Frequency of Neurological Involvement In Celiac Disease

| Author | Year | Country | Neurological involvement (%) | |
|---|---|---|---|---|
| [17] | 1966 | UK | 16/266 | 6% |
| [22] | 1971 | Ireland | 42/15 | 35.7% |
| [23] | 1999 | Finland | 10/144 | 7% |
| [24] | 2002 | UK | 189/620 | 30% |
| [25] | 2002 | Italy | 13/160 | 8% |
| [26] | 2004 | Israel | 18/148 | 12% |
| [27] | 2004 | Israel | 57/111 | 51.4% |
| [28] | 2008 | USA | 16/71 | 22.5% |

tations. The Frequency of neurologic system involvement in CD in these series reveals high degree of variation. This variation may not only be due to the environmental and ethnic factors, but also related to variable definitions and methodologies in different studies.

**Sex:** Hadjivassilliou and colleagues reported female to male ratio of the patients with neurological manifestations of CD as approximately 1:1 in one series [29].
**Age:** Neurological manifestations were more frequent in middle-aged adults, but rare in children [27, 30, 31]. In addition, the mean age at the onset of neurological manifestations was 48 years in one series [29].

**Pathology**

The pathological findings of CNS involvement in CD include lymphocytic infiltration (mainly T cell), especially in the spinal cord, hypothalamus, cerebellum, and brainstem [17,32], astrocytic gliosis, vacuolization of the neuropil of the cerebellar white matter [32], cerebellar purkinje cell loss [17,21,32,33], and demyelination in the posterior, lateral, and anterior cortico-spinal tracts in the cord [17,21]. Shams et al. reported extensive infiltration by medium sized cells with pleomorphic nuclei and prominent nucleoli in the cerebellar cortex and white matter which stained positively for CD45, CD3, and TIA-1 (cytotoxic granule marker) [34]. Moreover, Hadjivassiliou et al. found widespread Ig A deposition around the vessels in the brain of the patient with gluten ataxia. The deposition was most pronounced in the cerebellum, pons, and medulla [35]. In two CD patients with headache, autopsy results showed evidence of vasculitis [36].
The pathological findings in sural nerve biopsy of the patients with CD and neuropathy revealed changes of chronic axonopathy [37,38], wallerian degeneration, and degeneration-regeneration of nerve fibers [39].

**Pathogenesis**

Etiopathogenesis of the neurological manifestations of CD remains to be elucidated. There are cohorts of studies advocating the theory that gluten can affect cell function in cell culture systems, apparently in the absence of the immune system involvement. Gluten has shown this effect by inducing agglutination of K562(S) myelogenous leukemia cells, leading to actin rearrangement, and finally triggering apoptosis in Caco-2 cells [40]. Meanwhile, the presence of inflammatory reactions in the neural tissue of the postmortem pathological examination of the patients with CD and neurological complications led the investigators to think about an immunological mechanism, too [17,21,32]. In general, two speculated immunological mechanisms may explain the association between gluten sensitivity and neurological manifestations: Antigen molecular mimicry and Intermolecular help.

**Antigen molecular mimicry (Antibody cross -reactivity): The speculated mechanisms of molecular mimicry in the patients with gluten sensitivity are:**

1. Cross reactivity between gliadin species and gangliosides: Antigliadin antibodies may cross-react with Purkinje cells. Gliadin proteins and cerebellar Purkinje cells may share common epitopes. Such common epitopes have also been demonstrated to exist between gliadin proteins and enterocytes [41]. Up to 65% of the patients with celiac neuropathy had antibodies targeting one or more gangliosides [37,38]. It has been shown that some gluten species are glycosylates containing epitopes probably similar to ganglioside carbohydrates [42]. This may justify the induction of the antibody cross-reactivity. Moreover, in experimental studies, serum of the neurologically symptom-free CD patients demonstrated cross-reactivity with epitopes on Purkinje cells of both human and rat cerebellum [41]. Interestingly, elimination of antigliadin antibodies (AGA) from serum of the patients with CD and ataxia did not ameliorate the reaction to the Purkinje cells. This might have led the investigators to assume the presence of other antibodies against Purkinje cells in the patients with CD and cerebellar manifestations. Anti-ganglio

1. side antibodies may be the example. Alaedini et al. proposed synapsin I, a cytosolic phosphoprotein, as the target of cross reactivity with anti-gliadin antibodies in both central and peripheral nervous systems [43].
2. Predisposition to infection with organisms, such as Campylobacter jejuni or Haemophilus influenzae which have lipopolysaccharides similar to CNS or PNS gangliosides. This mode has analogies to the hypothesized pathogenesis of Guillain–Barre´ syndrome [44].
3. Another unknown mechanism: Investigations are still needed in order to approve this hypothesis and since there may be other unknown mechanisms involved in or facilitating the antibody cross-reactivity.

**Intermolecular help theory**

Gliadin molecules are deamidated by tissue transglutaminase (tTG). It has been speculated that tTG-specific B cells engulf the gliadin-tTG complex and present the gliadin portion to gliadin-sensitized T cells. The ensuing gliadin-reactive T cell helper could induce the ganglioside- specific B cells and produce anti-ganglioside antibodies in the absence of ganglioside-specific T cells [45].

**Clinical manifestations**

Neurological involvement in gluten sensitivity can be categorized into central and peripheral nervous system manifestations. The most common central nervous system manifestations include cerebellar syndromes, seizures, and dementias. Multiple sclerosis like presentations, motor neuron diseases, headaches, movement disorders, and neuro-psychiatric presentations, have been reported, as well. On the other hand, the peripheral nervous system involvement includes different types of peripheral neuropathies and muscular involvement. Mixed neurological syndromes are also prevalent; 45-68% of the patients with gluten sensitivity ataxia revealed electrophysiological evidences of neuropathy, too [29,32].

**Central nervous system involvement**

**1- Ataxia**

Gait and limb ataxia, myoclonus, occulomotor abnormalities, and dyarthria are the various cerebellar manifestations of CD. In a study by Hadjivassiliou et al., gait ataxia, lower limb ataxia, ocular signs, upper limb ataxia, and dysarthria were seen in 100%, 90%, 84%, 75%, and 66% of the patients, respectively [46]. Deconinck et al. reported a single case with opsoclonus- myoclonus associated with CD [47]. The frequencies of CD and gluten sensitivity in patients with ataxia of unknown origin have been reported between 1.9-15% and 12-47%, respectively [46,48,49]. In other studies, 13% of the patients with hereditary cerebellar ataxias and 23% of those with spinocerebellar ataxia type 2 had positive AGA [49-52]. On the contrary, some other studies showed no association between CD and idiopathic cerebellar ataxia [53-55]. Table 2 shows reports regarding the association between CD and epilepsy ataxia

**2- Seizures**

Several reports are available regarding the association between CD and epilepsy (Table 3). These studies did not separate drug-naïve epileptic patients from those who were on anti-epileptic drugs at time of study. As several anti-epileptic drugs induce the immune system and auto-antibodies are frequently seen in epileptic patients, clinical significance of this finding should be considered with caution. Gobbi et al. considered constellation of CD, epilepsy, and cerebral calcifications as a particular entity, CEC syndrome [56]. Efficacy of Gluten restriction seems to be inversely related to the duration of epilepsy and the young age of the patients. As cerebral calcification was not seen in the patients of Cronin et al. with epilepsy and CD, CEC syndrome may be a geographically based association rather than a distinct entity [57].

**3- Multiple Sclerosis**

In all [58-61] but one [62] case-control studies, no association was found between CD and gluten sensitivity, and MS. There are also

**Table 2.** Available Reports Regarding The Association Between Cd And Epilepsy Ataxia

| Study | Year | Country | Study Population | Study Type | Investigation | Major Findings | Major Conclusion |
|---|---|---|---|---|---|---|---|
| Hadjivassiliou et al. | 1996 | UK | 25 patients with Sporadic Ataxia | Descriptive | AGA, Biopsy | CD: in 16% of patients | gluten sensitivity is common in patients with ataxia of unknown cause |
| Pellecchia et al | 1999 | Italy | 24 patients with idiopathic ataxia 23 patients with hereditary ataxia | Descriptive | AEmA, AGA, Biopsy | CD: in 12.5% of patients with idiopathic ataxia And 0% of patients with hereditary ataxia | Association between CD and atxia |
| Combarros et al | 2000 | Spain | 32 patients with idiopathic ataxia | Descriptive | AGA,A EmA ARA, AtTGA | CD: in 0% of patients | No association between CD and atxia |
| Bushara et al | 2001 | USA | 26 patients with sporadic ataxia 24 patients with Hereditary ataxia | Descriptive | AGA,AEmA, ARA, AtTGA, Biopsy | +AGA: 27% of patients with sporadic ataxia, 37%of patients of hereditary cerebellar ataxia, Definite CD:? | Association between CD and ataxia |
| Burk et al. | 2001 | Germany | 104 patients with sporadic ataxia | Descriptive | AGA, AEmA, HLA, Biopsy | GS:10.6% of patients CD:1.9% of patients | Association between CD and ataxia |
| Luostarinen et al | 2001 | Finland | 44 patients with idiopathic ataxia | Descriptive | AGA,AEmA, AtTGA, Biopsy | CD:16.7% of patients | Association between CD and ataxia |
| Hadjivassiliou et al. | 2003 | UK | 59 patients with familial spinocerebellar ataxia 176 patients with sporadic idiopathic ataxia 33 patients with cerebellar variant of multiple system atrophy 1200 control | Case-control | AGA | GS:14% familial spinocerebellar ataxia 39% of sporadic idiopathic ataxia 15% cerebellar variant of multiple system atrophy 12% control CD in 24% of "gluten ataxia" | Association between CD and ataxia |



some case reports on the association between Neuromyelitis optica and CD [63,64].

### 4- Headache

In one study on pediatric age group [65] and one study on adults [66], CD was significantly more prevalent in the patients with migraine headaches in comparison to the healthy controls. Headac0he was also more prevalent in the CD patients compared to the healthy controls [67]. Besides, migraine and tension-type headaches were the most common types of headaches in the patients with CD [68]. Yet, adherence to GFD was efficacious in decreasing the frequency of headaches in some CD populations [36,67,69,70].

**Table-3.** Available Reports Regarding The Association Between Cd And Epilepsy

| Study | Year | Country | Study Population | Study Type | Investigation | Major Findings | Major conclusion |
|---|---|---|---|---|---|---|---|
| Chapman | 1978 | USA | 165 CD patients 165 controls | Case-control | Questionnaire | Epilepsy: 5.5% in CD patients, 0% in controls | Increased prevalence of epilepsy in coeliac disease |
| Fois et al. | 1994 | Italy | 783 patients with seizure disorders | Descriptive | AGA, AEmA, biopsy | CD: 2.3% in patients | |
| Cronin et al. | 1998 | Ireland | 177 with seizure disorders 488 controls | Case-control | AEmA, biopsy | GS: 2.3% in patients 0.4% in controls | Increased prevalence of gluten sensitivity in patients with seizure |
| Labate et al. | 2001 | Italy | 72 patients with childhood partial epilepsy | Descriptive | AGA, AEmA, biopsy | CD: 2.7% of patients | CD screening should be performed routinely only in patients with childhood partial epilepsy with occipital paroxysms |
| Luostarinen et al. | 2001 | Finland | 199 patients with epilepsy of unknown aetiology | Descriptive | serological screening, biopsy | CD: 2.5% in patients | Association between CD, epilepsy and brain atrophy |
| Essid et al | 2003 | Tunis | 49 patients with epilepsy | Descriptive | Biopsy | CD: 8.1% in patients | |
| Pratesi et al | 2003 | Brazil | 255 patients with epilepsy 4405 controls | Case-control | EmA, biopsy | CD:0.8 in patients 0.3% in controls | Not statistically significant increased prevalence of CD in epileptic patients |
| Pengiran et al | 2004 | UK | 801 CD patients | Descriptive | Interview, chart review | History of seizure: 2.6% in CD patients; active epilepsy:1.1% | No association between CD and active epilepsy |
| Rauna J et | 2005 | Finland | 968 patients with epilepsy 584Control | Case-control | AGA, AEmA, AtTGA | Only AGA IgA type was more prevalent in patients with primary generalized | |
| Dalgic et al | 2006 | Turkey | 70 pediatric patients with epilepsy 103 Controls | Case-control | AtTGA, Biopsy | CD:1.7% in patients 0% in controls | Association between CD and epilepsy in children |
| Antigoni etal | 2007 | Greece | 255 pediatric patients with epilepsy 280 controls | Case-control | AtTGA, AGA, ARA,AEmA, biopsy | GS: 1.9% in patients 0% in controls | Association between CD and epilepsy in children |
| Emami et al | 2008 | Iran | 108 epileptic patients | Descriptive | AtTGA, Biopsy | CD:2.8% of patients | Association between CD and epilepsy |
| Giordano et al | 2009 | Italy | 272 pediatric patients with epilepsy; 300 controls | Case-control | AGA, AEmA, AtTGA | GS:2.6% in patients In controls | No association between CD and epilepsy in children |
| Peltola et al | 2009 | Finland | 48 patients with therapy-resistant, localisation-related epilepsy | Descriptive | AGA, AEmA, AtTGA, HLA | GS:14.6% of patients | Association between gluten sensitivity, temporal lobe epilepsy and hippocampal sclerosis |
| Ertekin et al | 2010 | Turkey | 77 pediatric patients with epilepsy | Descriptive | AtTGA | GS: 15.6% of patients | |

Hadjivassiliou et al. considered the term "gluten encephalopathy" for the patients with gluten sensitivity, migraine-like headache, possible focal neurological deficits, and vascular type white matter Magnetic Resonance Imaging (MRI) abnormalities [36].

**5- Dementia**

There are a few case series about the association between dementia and CD [71,72]. In one study, the frequency of CD in Alzheimer's patients was not higher than the controls [73]. Furthermore, in another study, cognitive impairment was not found in CD patients [74]. Of course, both studies had been conducted on small sample sizes.

**6- Neuro-Psychiatric Manifestations**

Psychological reactions to a chronic disabling illness, such as CD, may interfere with the diagnosis of neurological complications. For instance, 19-35% of the patients with CD had a positive history of psychiatric diseases [75,76]. Although some studies revealed no associations between CD and schizophrenia in adults and autism in children [77-79], several authors have declared that an association may exist between CD and autism and between CD or gluten sensitivity and psychiatric disorders [14]. A few studies have also mentioned the efficacy of dietary intervention in autism [80-82].

**7- Movement Disorders**

Palatal myoclonus [21], opsoclonus-myoclonus syndrome [47], dystonia paralysis [83], Rhabdomyolysis [84], and choreathetosis [85,86] were reported in the patients with CD.

**8- Hearing loss**

Increased frequency of sensori-neural hearing loss in the patients with CD compared to the healthy controls was reported in two studies [87,88].

**9- Stroke**

There were case reports of stroke in the children and young adults with diagnosis of CD [89,90]. However, as the majority of these patients had other contributing factors, a cause and effect relationship between CD and stroke is a matter of debate.

**10- Spinal cord disorders**

In addition to the above mentioned case reports of neuro-myelitis optica with gluten sensitivity, isolated myelopathy has also been reported [91]. Goodman et al. reported that myeloneuropathy secondary to Copper deficiency occulted CD in the patient with progressive gait unsteadiness [92]. In addition, Hadjivassiliou et al. reported gluten sensitivity in 6/7 and CD in 1/7 of the patients with Stiff-Person syndrome, a syndrome which is a rare neurologic disorder with autoimmune characteristics. It is described by progressive, severe muscle rigidity or stiffness most importantly involving the spine and lower extremities [52,93].

**Peripheral Nervous System Involvement**

**1- Neuropathies**

Peripheral nervous system manifestations in CD include Guillain–Barre syndrome, predominately sensory polyneuropathy, mononeuritis multiplex, and autonomic neuropathy (Table 4) [38,94,95]. Of course, it should be mentioned that small fibers are more involved [95]. Celiac neuropathy commonly presents with paresthesia, dysesthesia, and areflexia. However, weakness and muscle wasting is less frequent.

In a population-based Swedish study, CD was significantly associated with only polyneuropathy, but not with other neuro-inflammatory or neuro-degenerative disorders [96]. The frequency of neuropathy in the patients with CD has been reported to be between 2.5-23%. Neuropathy is one of the most common neurological manifestations of gluten sensitivity [39,48]. The largest prospective study looking for the prevalence of gluten neuropathy showed that among the patients with idiopathic axonal peripheral neuropathy, 34% had circulating antigliadin antibodies. This value was reported as 12% in the healthy population [97]. Meanwhile, some other studies revealed no increased frequency of gluten sensitivity in the patients with idiopathic neuropathy [54].

**Table-4.** Available Reports Regarding The Association Between Cd And Neuropathy

| Study | Year | Country | Study Population | Study Type | Investigation | Major Findings | Major Conclusion |
|---|---|---|---|---|---|---|---|
| Hadjivassiliou et al. | 1996 | UK | 25 patients with sporadic PN | Descriptive | AGA, Biopsy | CD: in 8 % of ptients | gluten sensitivity is common in patients with neuropathy of unknown cause |
| Luostarinen et al | 2003 | Finland | 26 CD patients 23 controls | Case-control | Electrodiagnostic studies | chronic axonal neuropathy :23.1 % in patients 4.3 % in controls | increased occurrence of axonal neuropathy was observed in well treated celiac disease |
| Chin et al | 2003 | USA | 20 CD patients with neuropathy | Descriptive | Electrodiagnostic studies, sural nerve biopsy | Sural biopsy in three patients: mild to severe axonopathy. antiganglioside antibodies in 65% of patients | Association between CD and sensory neuropathy |
| Brannagan et al | 2005 | USA | 8 CD patients with neuropathy | Descriptive | Electrodiagnostic studies, epidermal nerve fiber (ENF) density | Normal NCV:7 patients Reduced ENF: 5 patients | sensory ganglionopathy or an immune-mediated neuropathy in CD |
| Lock et al | 2005 | UK | 32 patients with PN | Descriptive | AtTGA, HLA | GS: 0% | No association between CD and neuropathy |
| Gibbons and Freeman | 2005 | USA | 164 patients with suspected autonomic dysfunction | Descriptive | AGA, Biopsy | CD: 2.4% of patients | |
| Tursi et al. | 2006 | Italy | 32 CD patients | Descriptive | Electrodiagnostic studies, Antineuronal antibody | peripheral neuropathy:12 autonomicdysfunction:17, or both:3 patients pts | |
| Mata et al | 2006 | Italy | 220 patients with PN 110 patients with MND | Descriptive | AtTGA, nti-glycolipid antibodies | GS:2.7% in PN, 0.9% in MND | No increased risk of celiac disease |

PN: Peripheral neuropathy, MND: Motor Neuron Disease

**2- Myopathy**

Polymyositis [98-100], dermatomyositis [101], and inclusion body myositis [99] were reported to be accompanied with CD. Concomitant neuropathy and myopathy may be present, as well [99,102]. Treatment with immunosuppressive drugs and GFD was reported to be efficacious in this regard [99].

The role of gluten sensitivity in the patients with idiopathic neurological disorder

Some studies reported an elevated titer of Antigiladin antibody in the absence of intestinal involvement in a series of patients with neurological dysfunction of unknown cause [103]. Pellechia et al. revealed patients with CD who presented with idiopathic ataxia before any GI manifestation [104]. In one study, some patients with ataxia and elevated antigliadin antibodies responded to GFD [46].

The importance of undiagnosed gluten sensitivity in the patients with neurological disease of unknown cause is a matter of debate. Some researchers recommended IgG AGA as a part of the routine batteries for all the patients with neurological dysfunction of obscure etiology. On the other hand, other investigators decisively criticized this approach.

In the study by Hadjivassiliou et al., positive titers of antigliadin antibodies were more frequent in a heterogeneous group of patients

with neurological disease of unknown cause in comparison to the control group (The difference in proportion: 0.49 ,95% CI: 0.35-0.63). CD was found in 35% of the duodenal biopsies conducted in this sero-positve group [105]. Moreover, an epidemiological study of the prevalence of gluten ataxia suggested that it may account for up to 40% of the patients with sporadic idiopathic ataxia [46].

Conventional MRI showed cerebellar atrophy and white matter lesions in the patients with "gluten ataxia" [46]. MR spectroscopy patterns were also different between these patients and the control group [46]. That study also reported the presence of oligoclonal bands in up to 50% of the patients with gluten ataxia.

Gluten ataxia is the most common single cause of cerebellar ataxia among the patients with supposed idiopathic sporadic ataxia [46]. Recently, researchers found a novel transglutaminase, TG6, which was analog to TG2 and TG3 and was predominantly expressed in the CNS. Neurological presentation of gluten sensitivity in the absence of intestinal pathology can be justified by the role of this enzyme [106]. This team has also some genetic evidences for their speculation; 30% of general population, 90% of the patients with CD, and 70% of the patients with neurological disease and gluten sensitivity had HLADQ2 [29]. However, 20% of the patients with neurological disease and gluten sensitivity and none of the patients with gastrointestinal CD had and HLA DQ1 [106].

This may propose a genetic difference between the patients with neurological presentation and those with gastrointestinal presentation within the range of gluten sensitivity [29]. These findings led the "Shefield team" to consider "gluten sensitivity" as a heightened immunological responsiveness to ingested gluten in genetically predisposed individuals with or without intestinal pathology. Gluten ataxia forms a part of a spectrum of disorders associated with gluten sensitivity, including CD (gluten sensitive enteropathy) and dermatitis herpetiformis (gluten sensitive dermatopathy). Nonetheless, some investigators completely disagree with "Shefield School". In one study, neither the patients with idiopathic ataxia nor the patients with idiopathic neuropathy showed tTG Ab positively. Thus, they considered a reasonable doubt about the neurological status of "gluten ataxia" as a distinct disease entity [54]. In another study, high antigliadin antibody titers were found in 44% of the patients with Huntington's disease. This finding speculated that antigliadin antibodies in neurodegenerative diseases might be an epiphenomenon [107].

**Diagnosis**

Diagnosis is not troublesome when a relevant neurological syndrome occurs in a known case of CD. Diagnostic dilemma mostly appears in the patients who present with neurological problems and incomplete profile of CD or when history taking or physical examinations are not adequate and gluten sensitivity is neglected. MRI is by far the most beneficial imaging study for routine evaluation of neurological manifestations of CD.

**MRI**

Cerebellar atrophy and discrete white matter lesions were reported in the patients with CD [108,109].

**CSF**

CSF study of the patients with CD may reveal antigliadin antibodies [110].

**Treatment**

**Gluten Free Diet**

GFD is the milestone of treatment in serologically and histologically confirmed CD and neurological complications. To the best of our knowledge, no well controlled and prospective studies have been conducted to clarify the effects of GFD on idiopathic neurological disorders suspected to gluten sensitivity. The results of studies (mainly case reports) were also contradictive. Some studies [46,104] were in favor, while others [110,111] were against the therapeutic effects of GFD on the patients with ataxia suspected to gluten sensitivity. There were also contradictive results about administration of GFD to gluten neuropathy. Chin et al. did not find any objective improvement

with GFD [38], while Hadjivassiliou et al. found subjective improvement with GFD in the patients with idiopathic sensori-motor axonal neuropathy and circulating antigliadin antibodies [112]. There are some case reports on the response to GFD in the patients with epilepsy and cerebellar calcification [113-115]. Indeed, the beneficial effects of the diet have been reported as better seizure control and a decrease in antiepileptic drugs, but not complete remission of seizures [116]. There are also some reports on the positive effects of GFD on migraine headaches [36,66], neuropsychological problems [72,117,118], myopathy [30,119], and ALS associated with gluten enteropathy [118]. The effects of a GFD on these patients range from reversal of the dysfunction, stabilization of the illness, and even making little or no difference. Thus, it can be concluded that there is a therapeutic window of opportunity in which commencement of a GFD is helpful. It is very important to monitor the anti-gluten antibodies to know whether the lack of response relates to the lack of compliance or not. Antibody titers may remain high even 6-12 months after starting GFD. Duration of sustained GFD may also affect the response [52]. Ward et al. reported a 47 year old man with spinocerebellar degeneration associated with CD whose neurologic disorder initially deteriorated in spite of GFD, but stabilized after 4 months [120].

**Immunomodulatory treatments**

Administration of Intravenous Immunoglobulin (IVIG) or immunosuppressive drugs has been recommended in the patients with CD and neurological complications who revealed progression despite gluten free regimen. The therapeutic effects were contradictive, though. However, Souayah et al. [121] and Nanri et al. [122] found improvement with IVIG in three patients with biopsy-proven or antibody positive gluten sensitivity who developed cerebellar ataxia and /or neuropathic pain despite strict adherence to a GFD [121]. In another study by Nanri et al. and the study by Chin et al., the results were futile on celiac neuropathy [38,123]. Ait Ben Haddou and his colleagues reported a 41-year-old woman followed up for CD resistant to GFD who developed rapidly spastic paraparesis, cerebellar syndrome, horizontal diplopia, and decline of visual acuity. The diagnosis of neurological complications of CD was established and the patient was treated with methylprednisolone followed by oral prednisone. For 9 years, the patient's neurological signs were worsening at 15mg per day; however, the clinical status improved by increasing the dose to 30mg. The positive response to corticosteroids observed in this patient suggests an immunological mechanism [124].

**Conclusion**

Neurological manifestations in gluten sensitivity can be categorized into central and peripheral nervous system presentations. The most common central nervous system manifestations include cerebellar syndromes, seizures, and dementias. On the other hand, the peripheral nervous system involvement includes different types of peripheral neuropathies and muscular involvement. These presentations are uncommon in children but this prevalence in adult patients is as many as 36% [125].GFD is recommended for the patients with clinically, serologically, and histologically confirmed CD. There is a great controversy about the administration of GFD in the patients with neurological manifestations, without gastrointestinal presentation, and confirmed pathological evidence of CD in distal duodenal biopsy. There is no robust randomized clinical trial evaluating the long-term effects of GFD in these patients. GFD is recommended in the patients with histologically confirmed CD as well. For the patients with neurological manifestations, without gastrointestinal manifestations, and confirmed pathological evidence of CD in distal duodenal biopsy, the issue is much more complex. Small study sample size is the most important obstacle for judging about the presence or absence of "gluten ataxia/neuropathy" entities. Both pros and cons conducted studies on fewer than 100 patients. According to our review, it is reasonable that immunological screening should be conducted for the patients with headache, ataxia, and epilepsy, but not MS.

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