

## Neurological Manifestations of Celiac Disease

Ehsan Pishva<sup>1</sup>, Afshin Borhani Haghighi<sup>2✉</sup>, Soheil Ashkani-Esfahani<sup>3</sup>, Fereshte Bagheri<sup>3</sup>, Aliasghar Karimi<sup>3,4</sup>, Reza Malekzadeh<sup>5</sup>

<sup>1</sup>School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands

<sup>2</sup>Department of Neurology, Medical School, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>3</sup>Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>4</sup>Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran

<sup>5</sup>Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

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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

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### 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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Fax: +98 731 2227091  
PO Box 7461686688  
Email: info@gmj.ir



✉ **Correspondence to:**

Prof. Afshin Borhani Haghighi, Department of Neurology, Medical School, Shiraz University of Medical Sciences, Shiraz, Iran  
Telephone Number: +98917-7029134  
Email Address :borhanihaghighi@yahoo.com

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:** Hadjivassiliou 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, oculomotor abnormalities, and dysarthria 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 ataxia
Combarros et al	2000	Spain	32 patients with idiopathic ataxia	Descriptive	AGA, AEmA ARA, AtTGA	CD: in 0% of patients	No association between CD and ataxia
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 con-

trols. Headache 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 et al	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 ptiens	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-positive 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 “Sheffield 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 “Sheffield School”. In one study, neither the patients with idio-

pathic 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 contradictory. 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 contradictory 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 contradictory, 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 de-

veloped 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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