Review

Neurological Manifestations of Celiac Disease and Non-Celiac Gluten Sensitivity and the Effect of a Gluten Free Diet

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Abstract

Celiac disease (CeD) is an immune-mediated enteropathy triggered by gluten ingestion and affects nearly 1% of the population worldwide. CeD has typically been associated with gastrointestinal symptoms such as diarrhea and abdominal pain; however, its extra-intestinal manifestations are becoming widely recognized. In particular, CeD patients may present with various neurological manifestations and oftentimes, without evidence of gastrointestinal symptoms. The pathophysiology behind these manifestations is not well known, however, it is hypothesized that they may include vitamin deficiencies from malabsorption, direct gluten toxicity, and immune-mediated inflammation. The most common neurological manifestations include gluten ataxia, migraines, epilepsy, and neuropathies, but may also involve dementia, myopathies, and movement disorders. The first line treatment for CeD is typically a strict gluten-free diet, however its effect on neurological manifestations is less clear. Non-celiac gluten sensitivity/non-celiac wheat sensitivity (NCGS/NCWS) represents a condition where the ingestion of gluten causes symptoms similar to CeD, but CeD-specific enteropathy or serology are both absent. Several lines of research do not differentiate CeD and NCGS/NCWS and as a result, NCGS/NCWS is often under-studied. This study seeks to review the evidence regarding the neurological

manifestations of CeD, the effect of a gluten-free diet, and highlight studies investigating NCGS/NCWS as a distinct entity from CeD.

Keywords

Gluten, celiac disease, gluten sensitivity, wheat sensitivity, neurological disorders, extra-intestinal manifestations

1. Introduction

Celiac disease (CeD) is a chronic immune-mediated enteropathy of the small intestine that is triggered by dietary gluten intake in genetically predisposed individuals [1]. It is a relatively common disorder that affects nearly 1% of the population worldwide [2]. Studies investigating CeD have suggested a strong genetic component to its pathogenesis, as more than 95% of cases express the haplotypes HLA-DQ2 or HLA-DQ8. However, HLA-DQ2 and HLA-DQ8 haplotypes are present in up to 40% of the general population [3, 4]. Therefore, environmental factors such as intestinal infections, alterations in the gut microbiota, and age of gluten introduction are suspected to also play a role in the development of CeD [3].

Gluten, a storage protein found in wheat, barley and rye, precipitate immune-mediated inflammatory processes within the small intestine in patients with CeD [5]. The auto antibodies, anti-tissue transglutaminase, anti-endomysium, and anti deaminated-gliadin peptides, are typically associated with CeD and used for diagnosis [6]. As a result of the inflammation, CeD generally causes villous atrophy, crypt hyperplasia, and marked infiltration of lymphoid cells into the intestinal epithelium [7]. These alterations in mucosal architecture lead to a reduction in absorptive surface area and ultimately results in malabsorption. Due to the various histological changes in CeD, small bowel biopsy is often the gold standard for diagnosis. As a consequence of malabsorption, CeD typically presents with diarrhea, weight loss, abdominal pain, and steatorrhea [8]. However, the classical picture focussing on the intestinal symptoms of CeD has been decreasing over time; whereas its extraintestinal manifestations and asymptomatic presentations have been gaining prominence [8]. The extraintestinal manifestations of CeD are often multisystemic and include hematological, mucocutaneous, musculoskeletal, psychological, gynecological, and neurological conditions [9].

Gluten can also cause symptoms in the absence of CeD. NCGS/NCWS is a condition characterized by intraintestinal or extraintestinal symptoms following the ingestion of gluten in patients without CeD or wheat allergy [10]. In NCGS/NCWS, symptoms nearly mimic those of CeD; however, in contrast to patients with CeD, patients with NCGS/NCWS do not have the auto-antibodies or villous atrophy that is characteristic of CeD [11]. Due to lack of validated biomarkers, NCGS/NCWS can only be diagnosed after CeD is ruled out. In both CeD and NCGS/NCWS, the main treatment is strict life-long adherence to a gluten-free diet (GFD). Although not universal, strict adherence to a GFD typically results in the normalization of serological markers, improvement in intestinal mucosal abnormalities, and improvement of symptoms [4].

In the past few decades, the percentage of CeD and NCGS/NCWS patients that initially present atypically has been steadily increasing [12]. The uncertainty behind the extraintestinal

manifestations are further compounded as the pathogenesis of the many associated conditions are unclear. However, it is hypothesized that some may involve vitamin and nutrient deficiencies resulting from malabsorption, while others may involve various immune-mediated pathways [13].

Notably, the neurological manifestations of CeD are one of the major domains of investigation as patients may present with neurological disorders as their first or only symptom of CeD. It has been found that as many as 49% of CeD patients present with neurological changes [9]. These disorders include peripheral neuropathy, gluten ataxia, epilepsy, headaches, cognitive deficiency, and encephalopathy [9]. The prevalence of neurological symptoms in CeD patients is estimated to be approximately 8%, while a study conducted on patients with cryptogenic neurological disorders found that 57% had anti-gliadin antibodies (AGA), a non-specific antibody initially associated with CeD, and more recently to NSGS/NCWS [14, 15]. With delays in diagnosis and ultimately left untreated, patients could develop permanent neurological disabilities such as advanced dementia and irreversible damage such as Purkinje cell loss [16]. Therefore, it is important to consider CeD and NCGS/NCWS within the differential diagnosis when investigating for neurological disorders.

We have performed a review of the literature on the evidence regarding the neurological manifestations of CeD and NCGS/NCWS, and the effect of a gluten-free diet.

2. Materials and Methods

We searched the Medline (PubMed) database to identify studies involving the neurological conditions associated with CeD and NCGS/NCWS. The search strategy can be found in Supplementary data. We further screened the reference lists of included studies and related systematic reviews that were previously published to identify any additional relevant studies.

Studies were included regardless of study design, geographical location, and year of publication. We included studies up to April 2020, published in English, and additionally included those that reported the effects of the implementation of a gluten-free diet (GFD) on the neurological manifestations of NCGS/NCWS. Studies investigating psychological alterations, such as anxiety disorders and mood disorders, were excluded from this review. This review is primarily concerned with the investigation, summary, and critical analysis of the neurological manifestations of CeD and NCGS/NCWS and their relationship with the implementation of a GFD.

We assessed the quality of the body of evidence using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) [17]. GRADE specifies four levels of quality: high, moderate, low, and very low, based on five factors that ultimately decrease the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias. A summary of the main studies exploring the effects of a GFD for the neurological manifestations, and quality of evidence using GRADE approach for each neurological condition of CeD and NCGS/NCWS is shown in Table 1.

Table 1 Main studies exploring the effects of a GFD for the neurological manifestations of CeD and NCGS/NCWS.

Manifestation	Condition	Author (year)	Study design	Population	Outcome	GRADE score
Gluten ataxia	CeD	Mearns et al (2019)	Systematic Review	9 studies on gluten ataxia	Controversial findings; improvement in cerebellar functioning after GFD versus no improvements in self-reported ataxia assessments	Low (downgraded due to imprecision, inconsistency, and risk of bias)
		Hadjivassiliou et al (2017)	Prospective observational study	117 CeD patients with gluten ataxia	Improvement in cerebellar *N*-acetylaspartate /creatine levels	N/A
	NCGS/NCWS	Hadjivassiliou et al (2003)	Case-control study	43 patients with gluten ataxia	Improvement in every ataxia test metric and clinical impression	N/A
Migraines/ headaches	CeD	Zis et al (2018)	Systematic review and meta-analysis	40 studies in pediatric and adult CeD populations with headaches	Reduction in headache frequency in 51.6% - 100% of adult patients and 69.2% - 100% in children on a GFD	Low (downgraded due to risk of bias in the studies and large inconsistencies)
	NCGS/NCWS	Tovoli et al (2019)	Observational study	44 patients with NCWS (Salerno criteria)	Decrease in headache frequency after a GFD	N/A
Epilepsy	Mixed population of CeD and	Julian et al (2019)	Systematic review and meta-analysis	39579 pooled patients with epilepsy, CeD, or	Controversial; slight majority of patients in the included studies were responsive to a GFD (53% responsive, 47% non-responsive)	Low (downgraded due to high risk

				NCGS/NCWS		of bias in the included studies and inconsistencies)
	NCGS/NCWS			NCGS/NCWS		
Neuropathy	CeD	Mearns et al (2019)	Systematic review	13 studies on gluten neuropathy	Controversial findings; improvement in neuropathic symptoms after GFD implementation, but GFD adherence may not prevent or reverse neuropathic damage	Low (downgraded due to imprecision, inconsistency, and risk of bias)
		Tursi et al (2006)	Observational study	12 CeD patients with peripheral neuropathy	No differences in TNS/anti-neuronal antibodies from GFD versus baseline	N/A
		Simonati et al (1998)	Case report	1 child with CeD and progressive polyneuropathy	Progression in neuropathy despite GFD	N/A
	Mixed population of CeD and NCGS/NCWS	Hadjivassiliou et al (2006)	Case-control study	35 patients with gluten neuropathy	Improvement in sural SNAP amplitude and subjective neuropathy symptoms	N/A
		Hadjivassiliou et al (2010)	Retrospective observational case series	17 patients with sensory ganglionopathy	Stabilization in neuropathy symptoms after GFD adherence	N/A
		Zis et al (2017)	Case-control study	53 patients with gluten neuropathy	Improvement in pain and health change domains of SF-36 after GFD	N/A

3. Extraintestinal Manifestations - Neurological Disorders in CeD and NCGS/NCWS

3.1 Gluten Ataxia

Gluten ataxia (GA) is one of the most common neurological manifestations of CeD. It was initially defined as an idiopathic sporadic ataxia in the presence of anti-gliadin antibodies [18]. The main clinical manifestation of GA is characterized by the impairment of motor abilities. Patients typically present with difficulty with limb control, gait instability, abnormalities with eye movement, speech issues, and the loss of fine motor skills [19, 20]. Therefore, GA typically mimics the symptoms of pure cerebellar ataxia and often lacks clinical features that can distinguish the two [21].

GA frequently develops insidiously and is often not associated with the typical gastrointestinal symptoms of CeD [22]. In fact, typically less than 10% of patients with GA exhibit gastrointestinal symptoms and only a third have signs of enteropathy on biopsy. GA often develops in adulthood, affects both sexes equally, and has a mean age at onset of 53 years [23]. The prevalence of GA in CeD is estimated to be up to 6%, and constitutes 19%-41% of all neurological manifestations in patients with CeD [14, 19, 24, 25].

The underlying pathogenesis of GA remains unclear; however, a few theories have been postulated. It has been suggested that the anti-gliadin antibodies, or gliadin itself, could be directly neurotoxic to the cerebellum [26]. Another hypothesis postulates that it is vitamin E deficiency or autoimmune targeting of the cerebellum that is responsible for the development of gluten ataxia [27, 28]. The autoimmune hypothesis is supported by findings that suggest that the Purkinje cells of the cerebellum share similar epitopes with gliadin which may result in cross reactivity with anti-gliadin antibodies [26]. Overall, patients with GA typically have abnormalities that involve the cerebellum on magnetic resonance imaging (MRI) and magnetic resonance spectrometry [18]. These changes include cerebellar atrophy, loss of Purkinje cells, cerebellar inflammation, oligoclonal bands in the cerebrospinal fluid, and anti-Purkinje cell antibodies [29, 30]. In fact, cerebellar atrophy is found in up to 60% of patients with gluten ataxia, while nearly 100% have spectroscopic abnormalities that affect the vermis [18]. Diagnosis is typically based on clinical findings and confirmed if there is stabilization or improvement in symptoms after a GFD [31].

Early evidence behind the treatment of GA with a GFD has been controversial; especially case reports [29, 32]. However, recent studies in larger cohorts have demonstrated improvements in GA symptoms after following a GFD [33, 34]. A systematic review conducted by *Mearns et al.* further noted controversial findings and speculated that the differences may be due to the different methodology used to measure GFD adherence and neurological improvement [19]. Further, a study of 117 CeD patients with GA was separated into 3 groups; strict GFD adherence (negative serology), partial adherence (presence of AGA), or declined a GFD. A baseline magnetic resonance spectroscopy scan was compared to another scan after a mean interval of 22 months and demonstrated significant improvements in cerebellar *N*-acetylaspartate/creatine levels (a biomarker of neuronal functionality) after following a strict GFD [34]. Notably, the effect of a GFD was not dependent on the presence of enteropathy [33, 34].

Studies that investigate GA in patients with NCGS/NCWS is quite limited. A retrospective analysis of 334 patients with NCGS/NCWS (categorized by the authors as the presence of AGA in

the absence of enteropathy) and 228 patients with CeD presenting with neurological dysfunction found that 46% of NCGS/NCWS patients had GA compared to 41% in the CeD group [24]. The researchers noted that GA responded to a GFD in both groups. A more recent study evaluated anti-gliadin antibodies (AGA) in 31 patients with GA and found elevated AGA in 100% of the cases. According to the authors, this elevation in antibody levels was more frequently seen in NCGS/NCWS (classified as self-reported gluten intolerance, negative celiac serology, and the absence of villous atrophy) when compared to CeD (89 vs 48%) [35]. Further, a case-control study involving 43 patients presenting with gluten ataxia was conducted by recording ataxia test metrics and using a subjective global clinical impression scale [33]. After 1 year of following a strict GFD, confirmed by the elimination of anti-gliadin antibodies, there was an improvement in every metric measured compared to the control group.

3.2 Migraines/Headaches

Migraines are a commonly reported neurological complaint in patients with CeD and NCGS/NCWS. They are characterized as a recurrent headache disorder and can often drastically affect one's quality of life. Over 20% of people worldwide suffer from migraines at some point in their lives [36]. They typically present as a moderate to severe, unilateral, throbbing headache and involve nausea, vomiting, photophobia, or phonophobia [37]. Migraines have been documented as the initial and only manifestation of CeD in numerous studies [38-40].

In a large population-based study, the number of headache-related medical visits was compared between 28,638 CeD patients and 143,126 controls [41]. They found a higher percentage of CeD patients (4.7%) visited for headaches compared to the controls (2.9%). Further, a case-control study investigated 90 patients with idiopathic migraines and found that 4.4% had CeD compared to 0.4% in the controls [42]. Overall, patients with CeD are at a higher risk of developing migraines as demonstrated by a meta-analysis conducted by *Zis et al* [43]. They noted that the mean prevalence of headaches in adult patients with CeD was 26% and significantly higher when compared to controls (OR 2.7, 95% CI 1.7–4.3, $p < 0.0001$).

Imaging studies performed on patients with CeD complaining of migraines often show abnormalities. On computed tomography (CT) scans, there have been reports of occipital and parieto-occipital calcifications in patients with no evidence of epilepsy [44, 45]. On magnetic resonance imaging (MRI), there has been studies demonstrating white matter abnormalities in CeD patients with headaches [46]. A small study investigating single photon emission computed tomography (SPECT) of the brain found that all CeD patients had abnormalities suggesting cortical hypoperfusion [42]. Overall, the pathogenesis of migraines typically seems to involve brain hypoperfusion and perivascular inflammation [43].

The implementation of a GFD appears to be an effective treatment for migraines associated with CeD. A systematic review and meta-analysis demonstrated that the percentage of adults that report a significant reduction in headache frequency after GFD introduction ranges from 51.6% to 100%; and complete resolution is achieved in up to 75% [43]. Similar response rates were found in children and found that there was reduction in headache frequency and normalization of EEG findings after 6 months of a GFD [40, 47]. Further, it was demonstrated that strict adherence to a GFD for a period of 6 months (demonstrated by negative IgG anti-transglutaminase and negative IgA anti-endomysial antibodies) may normalize cortical hypoperfusion [42]. While patients who

adhere to a strict GFD (characterized by negative serology) have a lower incidence of white matter abnormalities [48].

NCGS/NCWS has been associated with recurrent headaches in a relatively low number of studies. An observational study involving 49 patients with self-reported gluten sensitivity found a greater proportion of headaches in the cases when compared to a group of 734 controls [49]. Further, various studies show that headaches seem more frequent in adults compared to children with NCGS/NCWS [50, 51]. Meanwhile, evidence regarding the effect of a GFD in patients with NCGS/NCWS and headaches is limited. A study involving 44 patients diagnosed with NCWS (confirmed by exclusion of CeD/wheat allergy and gluten-related symptoms that ameliorate after a GFD of at least 6 months) found that while 63.6% had headaches at baseline, this number decreased to 40.9% at a follow up of at least 1 year after GFD implementation [52].

3.3 Epilepsy

In both CeD and NCGS/NCWS, patients can present with variations of epileptic seizures with and without overt brain pathologies [16]. It is estimated that one-third of cases are refractory to treatment [53]. The symptoms of epileptic seizures vary markedly, however, they are associated with motor, sensory, and visual disturbances. Examples include hallucinations, abnormal sensations, twitching, loss of consciousness, and convulsions [54].

Results from a systematic review and meta-analysis found that the prevalence of CeD amongst individuals with epilepsy was 2.27% in adults, 1.83% in children, and 3.8% in studies with serological tests for general gluten sensitivity [55]. The overall pooled prevalence of epilepsy in patients with CeD was calculated to be 1.14%. These figures are consistently higher than what is found in the general population (0.64%) and suggest that there is an increased risk of epilepsy in CeD patients [53]. Similar to the other neurological manifestations, 40% of patients with CeD and epilepsy do not report having any gastrointestinal symptoms [55]. However, in contrast to the other manifestations which typically present later in life, epilepsy more commonly develops during childhood in patients with CeD [55].

The pathophysiology behind epilepsy in CeD patients is not fully understood. However, it is hypothesized that folate deficiency, immune reactions associated with anti-gliadin antibodies, and cerebral calcifications (CEC) play a role in its pathogenesis and are commonly found in patients with CeD and epilepsy [56, 57]. There are several different presentations of epilepsy in the context of CeD with CEC being the best characterized. CEC is a neurological syndrome where patients generally have focal, pharmacologically resistant epilepsy with parieto-occipital brain calcifications detected by CT or MRI [55]. In addition, patients with epilepsy and CeD may develop transglutaminase isoenzyme 6 (TG6) autoantibodies, hippocampal sclerosis with cell loss, cortical vascular and electroencephalography (EEG) abnormalities [58, 59]. Thus, diagnosis is typically established based on a combination of clinical, serological, EEG, and neuroimaging findings.

The implementation of a GFD could be an effective intervention to prevent epileptic seizures in patients with CeD. A systematic review of the literature demonstrated that the frequency of seizures decreased in 53% of patients with CeD following the introduction of a GFD [55]. However, cerebral calcifications associated with CEC may not resolve with the implementation of a GFD even after a follow up period of 2 years [60]. Research further suggests that the effectiveness of a GFD is inversely proportional to the duration of epilepsy prior to GFD introduction [16]. It is

hypothesized that the effects of a GFD result from the reduction of the neurological damage caused by gluten ingestion or the resolution of its malabsorptive sequalae with subsequent increase in folate, vitamin, and anti-epileptic drug absorption [49]. Therefore, this highlights the importance of early implementation of a GFD to improve the control of epilepsy in CeD patients.

Research investigating the association between epilepsy and NCGS/NCWS is extremely limited. A study conducted by Hadjivassiliou *et al* found that epilepsy and CEC are very rare in NCGS/NCWS patients with neurological dysfunction (1 out of 334 patients with AGA and no enteropathy) [24]. a single case-report study documented a two-year-old patient with epilepsy and NCGS/NCWS (based on clinical suspicion after exclusion of CeD and wheat allergy) that responded to a GFD which persisted at follow up after 2 years [61]. Therefore, further studies are needed to assess the relationship between epilepsy and NCGS/NCWS.

3.4 Neuropathy

Peripheral neuropathy (PN), is one of the most common neurological manifestations of CeD and NCGS/NCWS. [62]. The symptoms of PN include paresthesia, numbness, pain, muscle weakness, and autonomic symptoms [63]. The prevalence of PN in patients with CeD is estimated to be up to 49%; a risk 2.3-5.6 times greater than the general population [19, 64]. However, patients often present with neuropathic symptoms even before the diagnosis of CeD is made (4). A study further found that 2.5% of patients being investigated for idiopathic neuropathy had CeD [65].

The most common type of PN implicated in CeD is a chronic, symmetrical, sensorimotor peripheral neuropathy that primary affects the distal regions of the body [65, 66]. However, a wide variety of other neuropathic conditions have been reported, such as: sensory ganglionopathy, mononeuritis multiplex, pure motor neuropathy, a Guillain-Barré-like syndrome, and autonomic neuropathy [13, 65, 67]. Epidemiological studies investigating PN in CeD patients are limited, however, female sex and an increase in age is generally associated with an increased risk [19].

The pathogenesis of PN in the context of CeD has initially been thought to be as a result of vitamin deficiencies, potentially B_1, B_6, B_{12}, and E, and inflammation by direct gluten toxicity [13, 20]. However, recent reports suggest these factors may not play a significant role and it is more likely due to perivascular infiltration of immune cells that causes neurological damage [68]. Electrophysiological studies can be normal or only mildly abnormal in CeD patients with PN [69]. Skin and nerve biopsies have been found loss of myelinated fibers, axonal degeneration, and decreases in epidermal nerve density [68]. A study of 20 patients with CeD and PN found anti-ganglioside antibodies in 65% of cases [70]. These auto-antibodies may bind to Schwann cells, nodes of Ranvier, and peripheral nerve axons which may ultimately contribute to PN. On physical exam, the predominant manifestation of PN is a sensory neuropathy with variable involvement of large and small fibers [65]. Therefore, after the exclusion of other etiologies, diagnosis of PN may be established with a combination of diagnostic tests and clinical findings.

The effects of a GFD in CeD patients with PN is controversial. A systematic review conducted by *Mearns et al.* noted that although GFD implementation may improve neuropathic symptoms, it may not prevent or reverse neuropathic damage [19]. Further, a prospective study involving 35 CeD patients on a GFD found improvements in both sural sensory nerve action potential (SNAP) amplitude and in the patients' subjective assessment of their neuropathic symptoms [71].

Meanwhile, a case-control study of 53 CeD patients with neuropathy showed improvements in their pain and quality of life scores after strict GFD adherence (measured after negative celiac serology) [72]. Similar results have been noted in a retrospective study of 328 CeD patients followed for 2 years [73]. On the contrary, a small study found no significant differences in total neuropathy score (TNS) following 1 year of GFD implementation when compared to the baseline [74]. A study involving 10 patients without enteropathy also showed stabilization of PN symptoms after 6 months of strict GFD adherence; suggesting that the effect of gluten in PN may not be limited to the CeD population [75].

In a group of 334 patients with NCGS/NCWS (characterized as positive AGA and absence of enteropathy) and neurological dysfunction, the most common neurological manifestation found was peripheral neuropathy (54%) [24]. The researchers further noted that patients with CeD may have more severe PN when compared to NCGS/NCWS [24]. However, the vast majority of studies investigating neuropathy do not discriminate NCGS/NCWS from CeD. As a result, evidence supporting the association between PN and NCGS/NCWS is very limited. Further prospective studies in the NCGS/NCWS population are needed to determine the association with PN.

3.5 Others

Numerous studies suggest that there is an association between CeD and cognitive impairment [76, 77]. Oftentimes, patients may present with confusion, amnesia, attention difficulties, difficulties concentrating, and reduced mental acuity [78]. Several mechanisms for the pathogenesis of cognitive impairment in CeD patients have been postulated; including nutrient deficiencies, elevation in circulating cytokine levels as a result of systemic inflammation, and the direct effect of gluten on serotonin levels [79]. Transcranial magnetic stimulation (TMS) tests of the brain typically show hyper-excitability and impaired central motor conductivity [80]. Further imaging studies of patients with cognitive impairment associated with CeD may show brain atrophy, nonspecific gliosis, and nonspecific slowing on EEG [76]. The evidence regarding the effect of a GFD for cognitive impairment in CeD is mixed. Some studies suggest that cognition improves after GFD [76, 81] while others see the opposite effect [77, 82]. However, due to its potentially protective effect, authors typically suggest that a GFD should be introduced early.

Myopathies such as inclusion body myositis, polymyositis, and dermatomyositis are neuromuscular disorders that have been associated with CeD [83]. Studies suggest that the risk of an idiopathic inflammatory myopathy in CeD patients may be increased 9-fold when compared to the general population [83]. Like many other manifestations of CeD, it is speculated that myopathies may be related to an immune-mediated mechanism or vitamin deficiencies such as vitamin D or E [16]. Muscle biopsies in these patients may show muscle fiber necrosis, basophilic rimmed vacuoles, and inflammatory cell infiltrates [68]. Evidence generally suggests that clinical improvement could be attained with the implementation of a GFD for gluten-related myopathies [83-86].

A systematic review demonstrated that movement disorders such as chorea, dystonia, myoclonus, stiff-person syndrome, myokymia, paroxysmal dyskinesia, and myokymia are frequently reported in CeD [87]. The most common movement disorder noted was restless leg syndrome, possibly as consequence of iron deficiency, a finding that is commonly implicated in

CeD [87]. Studies suggest that restless leg syndrome symptoms typically improve with a GFD, with and without iron supplementation [88, 89].

In Figure 1 we summarized the prevalence and pathogenesis of the most common neurological conditions in CeD and NCGS/NCWS. Table 2 shows a summary of diagnostic methods and the effect of the gluten free diet on the most common neurological conditions in CeD and NCGS/NCWS.
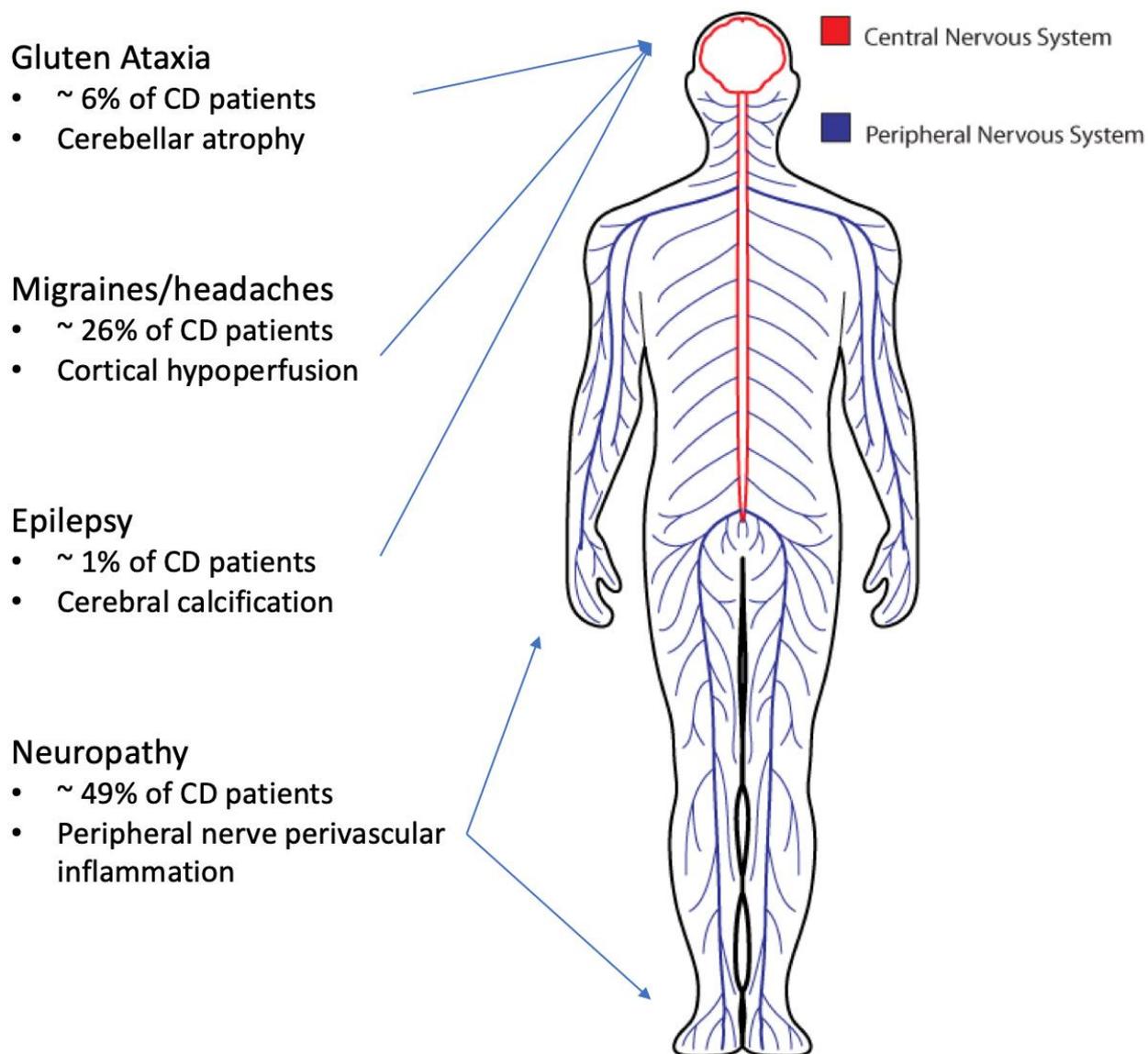

Gluten Ataxia
- ~ 6% of CD patients
- Cerebellar atrophy

Migraines/headaches
- ~ 26% of CD patients
- Cortical hypoperfusion

Epilepsy
- ~ 1% of CD patients
- Cerebral calcification

Neuropathy
- ~ 49% of CD patients
- Peripheral nerve perivascular inflammation

Central Nervous System

Peripheral Nervous System

Figure 1 Prevalence and pathogenesis of neurological manifestations in CeD and NCGS/NCWS.

Table 2 Summary of diagnostic methods and the effect of gluten free diet in the most common neurological manifestations of celiac disease and NCGS/NCWS.

Neurological Manifestation	Prevalence in CeD	Prevalence in NCGS/NCWS	Diagnosis	Effect of a gluten-free diet
Gluten ataxia	Up to 6% [19]	N/A	MRI, magnetic resonance spectrometry [18]	Controversial; In favour [32-34] Not helpful [29]
Migraines/headaches	26% [43]	12.2% - 63.6% [49-52]	CT [44, 45] MRI [46] SPECT [42]	In favour [40, 42, 43, 47, 48]
Epilepsy	Pooled mean of 1.14% [55]	Pooled mean of 0.93% [55]	CT, MRI [55] EEG and TG6 serology [58, 59]	In favour [55] Early intervention preferred [16]
Neuropathy	Up to 49% [19, 64]	54% of NCGS/NCWS patients presenting with a neurological complaint [24]	Electrophysiology studies [69] Skin and nerve biopsy [68] Anti-ganglioside serology [70]	Controversial; In favour [71-73, 75] Not helpful [74]

Abbreviations: N/A = Not applicable; MRI = Magnetic resonance imaging; CT = Computerized tomography; SPECT = Single photon emission computed tomography; EEG = Electroencephalogram; TG6 = Anti-tissue transglutaminase IgA 6; NCGS/NCWS= Non-celiac gluten sensitivity/non-celiac wheat sensitivity

4. Discussion

This review highlights the literature surrounding the prevalence, pathophysiology, diagnostic findings, and the effect of a GFD on the neurological manifestations of CeD and NCGS/NCWS. Peripheral neuropathy and migraines/headaches are generally known as the most common manifestations, followed by gluten ataxia and epilepsy. In all cases, the implementation of a GFD is typically recommended due to its low risk profile and potential benefits.

In addition to the neurological manifestations of CeD and NCGS/NCWS, a wide range of psychiatric symptoms and disorders including anxiety, mood disorders, and attention deficit hyperactivity disorder (ADHD) have also been found to be associated with gluten-related disorders [90]. The pathogenesis of these disorders are not fully understood, however, cerebral hypoperfusion, vitamin deficiencies, or neuro-inflammation could play a role [90]. Further, untreated CeD patients have been found to have neurotransmitter abnormalities including decreased plasma levels of tryptophan and monoamine precursors and decreased cerebrospinal fluid levels of serotonin and dopamine [90, 91]. Although the mechanisms of both the neurological

and psychiatric manifestations of gluten-related disorders are unclear, it could be speculated that the pathogenesis may follow similar mechanisms and should be further investigated.

Unfortunately, the overall quality of evidence for the studies reported are poor due to their observational nature. As a result, there are several limitations to this review. First, observational studies commonly involve selection bias during patient recruitment and publication bias as positive results are more likely to be published versus negative results. Further, many of the studies involved a relatively small number of patients which may make it difficult to estimate the true effect of GFD implementation. This limitation is further exacerbated by the clinical and methodological heterogeneities present in the reviewed studies. These include different definitions for the diagnosis of NCGS/NCWS, differences in follow up intervals (short intervals may miss neurological events such as a migraine) and differences in the definitions for the strictness of GFD adherence.

5. Conclusion

The classical picture of gastrointestinal symptoms has been fading in CeD and NCGS/NCWS, while the extra-intestinal manifestations are now well established. In particular, neurological manifestations have been increasing in prevalence and may often be the initial manifestation of CeD and NCGS/NCWS. Therefore, it may be beneficial to investigate for gluten-related disorders when a patient presents with a neurological condition of unknown etiology.

The treatment of gluten-related neurological manifestations with a strict life-long GFD immediately following diagnosis is generally recommended. However, the controversial findings suggest that further research is required to confirm the effects of a GFD for specific manifestations.

The vast majority of research on the neurological manifestations of gluten-related disorders refer primarily to CeD and are often confused with gluten sensitivity. Therefore, future large prospective studies with rigorous design methodology are needed to further investigate the association between both CeD, and particularly NCGS, and their neurological manifestations.

Supplementary Data

Medline (PubMed) Search Strategy

#1 (celiac* OR coeliac* OR celiac disease [MeSH]

#2 (non-celiac gluten sensitivity OR gluten sensitivity OR non-coeliac gluten sensitivity OR noncoeliac gluten sensitivity OR nonceliac gluten sensitivity)

#3 (#1 OR #2)

#4 (neurologic OR neurological OR neurological disorder* OR neurological manifestation* OR neurological complications)

#5 (gluten ataxia OR migraine OR headache OR epilepsy OR neuropathy OR cognitive disorder OR cognition)

#6 (#4 OR #5)

#7 (gluten free OR gluten-free OR gluten-free diet OR gluten free diet OR GFD)

#8 (#3 AND #6 AND #7)

#9 (#8 AND Filters: Clinical Trial; Comparative Study; Controlled Clinical Trial; Meta-Analysis; Observational Study; Randomized Controlled Trial; Review; Systematic Reviews; Publication date from 1995 – 2020; Humans; English

Yield n=90

Author Contributions

MIPS conceptualized the study and reviewed the manuscript. JZ performed the literature review and wrote the manuscript. Both authors approved the final version of the manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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