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Review Article

Diagnostic and Treatment Options to the Patients Presenting with Neurological Symptoms Caused by Celiac Disease

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Summary. Celiac disease (CD) is a gastrointestinal disorder caused by the immune system's response to gluten, involving both innate and adaptive immune reactions. It leads to various neurological issues, such as gluten ataxia, gluten neuropathy, epilepsy, and gluten encephalopathy. Although neurological presentations are rare in children, they are observed in up to 36% of adult patients with CD. Recent evidence suggests that these manifestations may be linked to gluten-related mechanisms, including antibody cross-reactions, immune-complex deposition, direct neurotoxicity, and, in severe cases, vitamin or nutrient deficiencies. However, there is still no consensus on whether serological, neurophysiological, or neuroimaging findings can effectively diagnose and monitor CD-associated neurological problems at an early stage. The identification of multimodal biomarkers and suitable neuroimaging tools could aid in the diagnosis, monitoring, and enhancement of the quality of life for individuals with neuroceliac disease. Nonetheless, it is essential to provide appropriate treatment to those with CD and neurological symptoms, as prolonged suffering may lead to irreversible disability. The primary treatment for neurological manifestations of gluten-related disorders is a strict gluten-free diet, although a small number of patients may require additional immunosuppressive therapy, typically using mycophenolate or intravenous immunoglobulins. In this literature review, our aim was to explore the relevant neurological disorders associated with CD, early diagnostic and treatment options to prevent related disability in affected patients. Clinicians should consider CD as a potential cause in individuals presenting with unexplained neurological dysfunction.
Keywords: Celiac disease, gluten ataxia, gluten neuropathy, epilepsy, gluten encephalopathy, diagnosis, treatment.

Pacientų, turinčių celiakijos sukeltų neurologinių simptomų, diagnostikos ir gydymo galimybės

Santrauka. Celiakija yra imuninės sistemos sukeliamas virškinimo sistemos sutrikimas, kuris atsiranda dėl į gliuteną nukreiptos imunogeninės reakcijos.

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Gliuteno sukeliamos imunogeninės ir neurotoksinės reakcijos nulemia įvairius neurologinius sutrikimus, tokius kaip gliuteninė ataksija, gliuteninė neuropatija, epilepsija ir gliuteninė encefalopatija. Šios neurologinės apraiškos vaikams yra retos, bet jų gali būti net iki 36 % suaugusiųjų, sergančių celiakija.

Naujausi tyrimai rodo, kad neurologinius sutrikimus sergant celiakija gali sukelti su gliutenu susiję patogeneziniai keliai, tokie kaip antikūnų „cross-reactions", imuninių kompleksų kaupimasis, tiesioginis neurotoksiškumas ir sunkiais atvejais vitaminų ar maisto medžiagų trūkumas. Vis dėlto dar nėra sutarimo, ar serologiniai, neurofiziologiniai, neurovaizdiniai tyrimai gali padėti efektyviai diagnozuoti ir monitoruoti su celiakija susijusias neurologines ligas ankstyvose jų stadijose. Specifinių biožymenų ir tinkamų neurovaizdinių tyrimų identifikavimas gali padėti diagnozuoti, monitoruoti ir pagerinti gyvenimo kokybę pacientams, sergantiems neuroceliakija. Maža to, yra be galo svarbu suteikti optimalų ir ankstyvą gydymą individams, sergantiems celiakija, kai yra neurologinių simptomų, nes nepalengvinta šių simptomų našta gali sukelti negrįžtamų sutrikimų ir negalią. Svarbiausias neurologinių manifestacijų gydymas pacientams, sergantiems celiakija, yra griežta dieta be gliuteno, tačiau nedideliam skaičiui pacientų gali prireikti papildomo imunosupresinio gydymo, dažniausiai pridėti mikofenolatą arba intraveninių imunoglobulinų. Šioje literatūros apžvalgoje siekėme pabrėžti neurologinės kilmės sutrikimus sergant celiakija, ankstyvas diagnostikos ir gydymo priemones, kad būtų išvengta negrįžtamos žalos pacientui. Gydytojai turėtų apsvarstyti celiakiją kaip galimą priežastį tiems pacientams, kuriems pasireiškia nepaaiškinami neurologiniai sutrikimai.

Raktažodžiai: celiakija, gliuteninė ataksija, gliuteninė neuropatija, epilepsija, gliuteninė encefalopatija, diagnostika, gydymas.

Introduction

Gluten related disorders (GRDs) encompass a range of manifestations that all share a common trigger – the ingestion of gluten (1). The known and extensively studied disorder, in this category is celiac disease (CD), also known as gluten sensitive enteropathy. CD is an immune mediated enteropathy affecting the small intestine. It occurs in individuals who have a genetic predisposition and consume gluten (2). An autoimmune condition, not an allergy or sensitivity, makes it distinctly different from gluten intolerance. Studies conducted worldwide indicate that CD has a prevalence of 1.4% (3). While gastrointestinal symptoms, such as diarrhea, abdominal pain, bloating and vomiting, are commonly associated with CD, many patients also experience other manifestations: anemia, dermatitis herpetiformis, neurological symptoms, etc. (4). Notably, neurological changes are particularly relevant to consider in CD patients since up to 36% of adult patients with CD present with neurological disorders (5). There have been various neurological conditions associated with CD, with the most common ones being ataxia, epilepsy, encephalopathy, and peripheral neuropathy. It is worth noting that while CD generally affects females more frequently than males (with a ratio of about F 2.4:1 M), when it comes to gluten related neurological disorders, men seem to be affected more frequently (57%) (6). The typical age at which these neurological complaints start is around 50.3 years (6).

Interestingly, many individuals with neurological symptoms do not manifest gastrointestinal symptoms (7). Because of the lack of gut involvement in these patients, neurocoeliac disease may easily go unrecognized (7). If not diagnosed early or if the adequate treatment is not administered, a patient may face a permanent neurological disability. Also, there is still uncertainty regarding which particular serological markers or a combination of markers should be used in diagnosing gluten related disorders. Additionally, the determination of the imaging tools that are most effective in diagnosing these disorders still remains a challenge. The diagnosis itself holds importance as it enables healthcare professionals to choose correct treatments for the ongoing neurological symptoms and ultimately improve the patient's quality of life and outcomes. In this literature review, our goal is to raise awareness among clinicians about the neurological manifestations seen in CD patients. Furthermore, we aim to provide insights into the treatment options and essential diagnostic tools for

such conditions as ataxia, peripheral neuropathy, epilepsy and gluten encephalopathy in individuals with CD.

Etiopathogenesis

The causes and mechanisms behind the involvement in CD are still a subject of debate. Recent evidence suggests that particular factors may play a role in gluten-mediated pathogenesis, including the possibility of antibody cross reactions, deposition of immune-complex, direct neurotoxicity, and, in severe cases, deficiencies in vitamins or nutrients (8). The immune response is a detrimental component in the development of CD. It has been well documented that 90% of CD patients have the leukocyte antigen HLA DQ2 or HLA DQ8 allele. Gliadin, a protein found in gluten, is considered the culprit in CD pathogenesis (9). It undergoes deamidation by tissue transglutaminase (tTG), which enables it to be recognized by antigen presenting cells (APCs). This triggers a T cell mediated hypersensitivity reaction and leads to histological changes in the small intestine, such as an increased number of lymphocytes in the lamina propria, crypt hyperplasia, and the flattening of the intestinal villi (10).

Recent research suggests that the neurological symptoms associated with CD may also be caused by immune processes. A post-mortem study of individuals with gluten ataxia found that Purkinje cells are lost throughout the cerebellar cortex, and that there is diffuse T lymphocyte infiltration in the cerebellar white matter, as well as inflammation around the blood vessels (11). Similar lymphocyte infiltration with inflammation has also been observed in the peripheral nervous system, particularly in sural nerve biopsies from subjects with gluten neuropathy (12). Antibodies (AB) to TG6, which is expressed by activated astrocytes, microglia and neuronal cells in the brain, have been identified in up to 85% of celiac patients with neurological symptoms (13), and TG6 shares a degree of genetic and functional similarity to intestinal transglutaminase 2 (14). Anti-TG6 AB in CD patients has shown reactivity towards deep cerebellar nuclei, brainstem structures and cortical neurons, which leads to cross-reactivity with neuronal cells, and results in lesions (14). In glutenic neuropathy, axonal degeneration is induced by gliadin antibodies via an inflammatory vasculopathy mechanism. In addition, a high proportion (80%) of individuals with sporadic neuropathy exhibit HLA types that correspond to CD patients (15).

Gluten ataxia

Gluten ataxia is one of the most frequent neurological abnormalities in celiac disease. It affects 6% of CD patients and increases up to 40% for those who experience neurological symptoms (5). Among the causes of sporadic ataxia, GA stands out as the most prevalent case, accounting for about 25% of cases (16). Its predominant clinical manifestations include dysarthria, dysphonia, pyramidal signs, abnormal movements of eyes, and progressive ataxia of gait (6). With the average age of onset being 48 years, patients usually present with pure cerebellar ataxia, primarily affecting their lower limbs (90%) and upper limbs (75%) (17). Interestingly, fewer than 10% of GA patients report gastrointestinal issues, although nearly half of them show signs of CD upon small intestinal biopsy (18). This means that ataxia related to CD is not often associated with the typical gastrointestinal symptoms or malabsorption signs. Gluten ataxia is associated with immune mediated reactions involving anti-gliadin and anti-endomysium antibodies, as well as the HLA DQB1*0201 haplotype (6). It is believed that the loss of Purkinje cells in ataxia may be caused by an immune mediated process, for instance, anti-TG6, anti-gliadin and anti-endomysium antibodies which are associated with ataxia (19). CD patients with GA often exhibit oligoclonal bands in their cerebrospinal fluid. This indicates perivascular inflammation in the cerebellum (20). Another theory suggests that gluten toxicity itself

and a deficiency in vitamin E could be contributing factors and should be further investigated (20). Patients with GA typically show signs of cerebellar atrophy, particularly affecting the cerebellar vermis, when examined via MR imaging. MR spectroscopy has shown abnormalities in the vermis for 60% of patients with GA (21). The current recommendation is to screen individuals presenting with GA for sensitivity to gluten by using such antibodies as anti-gliadin IgG and IgA, anti-EMA, anti-TG2 and anti-TG6. Adopting a GFD usually leads to clinical improvement.(18).

Gluten neuropathy

Gluten neuropathy (GN) refers to an idiopathic sporadic neuropathy, but with indications of sensitivity to gluten, based on serological evidence (22). Various types of Celiac disease neuropathies have been identified, including small fiber sensory neuropathy, symmetric predominantly sensory neuropathy, mononeuritis multiplex and multifocal motor or sensorimotor polyneuropathy (23).

The prevalence of GN in patients with CD ranges from 0% to 39%, with older individuals and females being at a higher risk (11). Research suggests that around 50% individuals with CD may experience some form of peripheral neuropathy (23). However, only one third of those with GN show evidence of CD on biopsy (23). The most common type of gluten related peripheral neuropathy is a symmetrical sensorimotor axonal length dependent condition, found in approximately 75% of cases, followed by sensory ganglionopathy, an asymmetric form of pure sensory neuropathy, where the pathology is located within the dorsal root ganglia (24). During examination, sensory neuropathy is the predominant manifestation observed in patients with CD, involving both large and small nerve fibers; however, small nerve fibers tend to be affected more (25). Normal nerve conduction, while permanent and intense pain along with a loss of sensation is manifested, indicates the presence of small fiber neuropathy (SFN), which could potentially be an early sign of GN (26). Electrophysiological studies, as well as sural nerve or skin biopsies, may be abnormal, and anti-ganglioside autoantibodies may be detected (27). These autoantibodies may attach to Schwann cells surfaces, nodes of Ranvier, and peripheral nerve axons (27). Research has indicated that adhering to a GFD may lead to improvements in GN for individuals with the most common forms of neuropathy, in this case, with length dependent sensorimotor axonal peripheral neuropathy or sensory ganglionopathy (28).

Seizures

Around 5.5% of individuals with CD experience seizures (29). Focal unaware seizures are the most common type observed, although generalized seizures can also occur (6). It has been proposed, that CC, HS lesions, notably, folic acid deficiency or an autoimmune phenomenon, are often associated with white matter abnormalities in those with CD (26,30). Additionally, a connection has been found between CD, localization related epilepsy and occipital cerebral calcifications, known as '*Celiac disease, epilepsy and cerebral calcifications syndrome*' (CEC) (31). Patients with CEC may experience visual symptoms, such as blurred vision, difficulty focusing, visualized colored dots, or brief stereotyped complex visual hallucinations (30). It is worth noting that patients with cerebral calcifications and epilepsy who do not present histological evidence of celiac disease share the same HLA phenotype as those diagnosed with CD. Additionally, a study revealed an association between gluten sensitivity and TLE with HS: 48 patients with epilepsy, who were resistant to ASMs, underwent testing for gluten sensitivity and received a duodenal biopsy. Out of 16 patients with TLE and HS, 7 (44%) showed gluten sensitivity, whereas none of the patients with TLE without HS or extratemporal epilepsy displayed gluten sensitivity. Furthermore, 3 out of 7 patients exhibited features of CD on duodenal biopsy. In terms of treatment options, following GFD can be beneficial in managing seizures, especially when implemented soon after the onset of epilepsy (32).

Gluten encephalopathy

The prevalence of gluten encephalopathy has not been yet documented. It is associated with white matter lesions (WML) on MRI scans and headache symptoms which occur from 30% to 56% patients with CD and which seems to decrease when patients adhere to a free diet (33). The most common types of headaches in patients with CD are tension-type and migraine-like headaches. Tension type headaches manifest as bilateral, dull, and constant head pain, while migraine-like headaches present as severe headaches, usually accompanied by nausea, vomiting and photophobia. A clinical study aiming to characterize headaches in patients with CD revealed that, out of 866 patients with CD and headaches, 52% complained about tension-type headaches, and 32% suffered from migraine-like headaches (34). The white matter abnormalities observed in CD patients can be diffuse or focal, and sometimes they may not fully resolve after adopting GFD, but rather only stop progressing further. The cause of the condition is not clear, but isolated vasculitis has been found on brain biopsy, which indicates the autoimmune origin (35). Other possible explanations include deficiencies in vitamins and minerals due to malabsorption (35). Additionally, patients with CD have shown altered blood flow to the brain, which could potentially lead to gluten encephalopathy (36). A study using positron emission tomography (PET) brain imaging found that 73% of CD patients who were not following GFD displayed a reduced blood flow in at least one region of the brain compared to only 7% of healthy controls and in CD patients on GFD (36).

Diagnostics

Accurately diagnosing CD requires an evaluation which would combine clinical assessments, serological tests, and histopathological examinations. It is recommended that individuals showing symptoms of CD should undergo serological testing. Various AB, such as tissue transglutaminase (Anti-tTG), anti-endomysial (EMA), anti-deamidated gliadin peptides (Anti-DGP) IgA/IgG antibodies, can be used in the detection of CD (37). The gold standard for diagnosing CD involves an antibody test followed by a small intestinal biopsy evaluation. In order to ensure a diagnosis, it is important to obtain adequate samples from the small intestine. Studies have found that at least one biopsy from the duodenal bulb and a minimum of four biopsies from the distal duodenum are necessary for an accurate diagnosis (38). When serological and histopathological test results are inconclusive, HLA typing can be used to help determine if CD is present. HLA DQ2/DQ8 are the most important genetic risk factors associated with CD. Since almost all individuals with CD possess these HLAs, their absence makes the diagnosis of CD highly unlikely. The HLA DQ2 variant is commonly found in 90–95% of CD patients, while the remaining 5% have the HLA DQ8 variant (39). Even if there are no intestinal lesions, patients with neurological symptoms may still have circulating anti-DGP and anti-tTG antibodies (39). Transglutaminase-6 (TG6), which is produced by activated astrocytes, microglia and other neurons in the nervous system (CNS), is considered an autoantigen and an initial indicator of neurological involvement in gluten related diseases, especially in gluten ataxia. Due to this reason, anti-TG6 has been proposed as a sensitive and specific biomarker for the diagnosis of gluten-related diseases (14).

Gluten ataxia main diagnostic tools

Researchers have suggested that TG6 autoAB may serve as an early indicator of neurological involvement in gluten-related diseases: they have detected TG6 AB in the blood of patients with gluten ataxia (73%), gluten neuropathy (50%), regardless of enteropathy (14). In fact, they have observed IgA deposits against TG6 in vessels from cerebellar tissue of a patient with gluten ataxia (40). Also, it

is recommended that individuals presenting with cerebellar ataxia should undergo screening for gluten sensitivity by using antigliadin IgG and IgA, anti-TG2 AB, and, most importantly, anti-TG6 AB. Those patients who test positive for any of these AB without a clear alternative cause for their ataxia should be advised to follow a GFD and receive regular follow-up to ensure antibody elimination. This process typically takes 6–12 months (18). If the patient's ataxia stabilizes or even improves after one year, it strongly indicates a diagnosis of GA (35). Radiological investigations can also be used to diagnose GA. One way to investigate this is through magnetic resonance spectroscopy (MRS) of the cerebellum, which measures N acetyl aspartate/creatine (NAA/C) area ratios. NAA/C serves as a marker of neuronal health. It has been found that 60% of GA patients show cerebellar atrophy when examined by using MRS (21). Even in patients without cerebellar atrophy, abnormal results were observed in proton MRS of the cerebellum. A study investigating the serology marker anti-TG6 found that 28 out of 38 (73.7%) TG6+ patients had abnormal results in cerebellar MR spectroscopy (41).

Gluten neuropathy main diagnostic tools

To diagnose GN, doctors look for the presence of ganglioside AB in patients without any cause for their neuropathy (17). Molecular mimicry between ganglioside molecules of peripheral nerves and gluten is a proposed mechanism, and antiganglioside ABs were present in the serum of 65% of a small cohort of CD patients with neuropathy (23,42). These autoAB may attach to Schwann cells, nodes of Ranvier, and peripheral nerve axons (27). Additionally, regardless of enteropathy, in up to 50% of individuals with GN, anti-TG6 can be detected. In order to confirm the diagnosis of GN, it is recommended that all patients should undergo nerve biopsies. These biopsies typically demonstrate non-length-dependent pattern and show mild to moderately severe chronic axonopathy with loss of myelinated fibers (42). Electro-diagnostic studies usually appear normal in individuals with GN, for instance, normal nerve conduction, while permanent and severe pain along with sensory loss is observed. It suggests the involvement of small nerve fibers and could be considered as early signs of CD (26). Sudoscan has also been used in studies to diagnose neuropathy in patients with CD. Sudoscan offers a non-invasive, objective and measurable approach to evaluate the sudomotor function by measuring electrochemical skin conductance (43). One study diagnosed small fiber neuropathy by using Sudoscan in 32 individuals with CD (43). Sudomotor dysfunction is seen as one of the symptoms that appear earlier in neuropathies of distal small fibers. Therefore, evaluating the sudomotor function is a way to assess and monitor small fiber neuropathy.

Epilepsy main diagnostic tools

Firstly, it is recommended that patients who have both CD and epilepsy should undergo laboratory assessments. Research studies have shown the presence of autoantibodies, such as anti-tTG, anti-endomysium and anti-reticulin in individuals with epilepsy (44). Imaging studies commonly reveal cerebral calcifications or hippocampal sclerosis in patients with both CD and epilepsy. The occurrence of cerebral calcifications in individuals with CD has been associated with epilepsy and is often referred to as *CEC syndrome* (45). CEC syndrome typically manifests as a focal or complex partial type of epilepsy, usually originating from the occipital lobe. While the exact prevalence of CEC syndrome remains unknown, one study analyzed 171 literature cases of CEC and found that 127 patients had epilepsy (31). MR findings show bilateral cortical and subcortical occipital calcification and a smaller percentage in the frontal, temporal areas, the absence of lobar or hemispheric atrophy, and the absence of contrast enhancement not associated with atrophy or vascular anomalies (46). Pathologically, these calcifications consist of pial angiomas, fibrosed veins and large microcalcifications containing calcium and silica substances (47). The range of electroencephalography (EEG)

features associated with CD is quite extensive. Wakefulness EEG has reported focal activity, such as unilateral or bilateral spikes or slow waves, primarily localized in the occipital regions (48). One study has explored the prevalence of neuronal hyperexcitability and subclinical EEG abnormalities in 47.4% asymptomatic children newly diagnosed with CD (49). Based on these ideas, some authors have referred to it as 'hyperexcitable brain' in CD (12).

Gluten encephalopathy main diagnostic tools

MRI is considered the effective imaging technique to identify encephalopathy. Abnormalities observed in MRI scans can range from areas of an increased signal intensity across the white matter to scattered spots of a high signal intensity in both hemispheres (33). Among patients with gluten encephalopathy, the common findings were white matter abnormalities (WMA). In one study, a case series of 10 patients with CD presented with episodic migraines in association with WMA was investigated (33).

Functional imaging studies, such as single photon emission computed tomography (SPECT), can also contribute to the diagnosis of gluten encephalopathy. A case controlled study involving four adult patients diagnosed with CD and experiencing migraines revealed abnormalities in regional cerebral blood flow patterns (50). In all cases, a circumscribed area of cortical hypoperfusion was present, whereas there were no interhemispheric asymmetries of the cortical regional blood flow in five migraine patients without evidence of CD. Another study also provided evidence indicating changes in the cerebral blood flow (36). The researchers observed the patients for a duration of one year by conducting SPECT scans. They discovered that, among 15 patients with CD who followed a GFD, only one patient experienced a reduced blood flow in at least one brain region. On the other hand, out of 15 untreated CD patients, 11 individuals developed a hypoperfused region in the brain.

Treatment

Nowadays, the effective treatment option for patients with CD follows a GFD. It has been observed that more than 90% of patients experience improvement when they adopt a gluten-free strategy. However, the main reason for the failure of gluten diets is due to continued consumption of gluten. The remaining 10% of individuals are referred to as patients with refractory CD or refractory sprue. This particular group consists of those who respond positively to restricting dietary proteins, such as soy, respond to glucocorticoids, develop gradual improvement after months or years, and fail to respond to all sorts of interventions (6). When it comes to gluten related manifestations, it is crucial for individuals to begin strictly adhering to a GFD as soon as possible (18). In cases involving these diseases, except for such conditions as cortical myoclonus and advanced dementia, adoption of a strict GFD showed positive therapeutic effects. Immunosuppression treatments are only considered if strict adherence to a GFD does not yield beneficial results and in cases where patients have refractory celiac disease (18).

Gluten ataxia treatment

GFD is the primary treatment for GA. The effectiveness of GFD varies depending on how long a person had been experiencing ataxia before being diagnosed with CD. In a systematic case-controlled study involving 40 patients with ataxia, some with and some without enteropathy, it was shown that those who were strictly following a GFD and had evidence of eliminating gliadin antibodies experienced significant improvement in ataxia test scores compared to the control group who did not adopt a GFD (28).

In addition to improving symptoms in patients with GA, an extensive study involving 117 patients revealed that following a GFD also had positive effects on MR spectroscopy parameters (51).

In particular, the ratio of N-acetylaspartate (NAA)/creatine (Cr) in the cerebellar vermis was increased in 62 out of 63 patients (98%) who strictly followed a GFD (with eliminated anti-gliadin AB). Among the patients on GFD, but still positive for AB, only 9 out of 35 (26%) showed an increased NAA/Cr ratio. In contrast, only 1 out of 19 patients (5%) who were not on GFD exhibited an increased NAA/Cr ratio. These findings regarding the NAA/Cr ratio after adhering to a strict GFD further support the previous observations of clinical improvement in ataxia among patients with GA.

In cases where a year-long adherence to GFD does not lead to any improvement in ataxia or if ataxia worsens rapidly, such treatment options as immunosuppressants and intravenous immunoglobulins (IVIG) may be considered (18). A small uncontrolled case series involving 4 GA patients reported a positive effect from intravenous immunoglobulin treatment (22). Additionally, another study highlighted five refractory to GFD GA patients with myoclonus (52). All five patients received mycophenolate with one patient receiving rituximab and IVIG. The response to immunosuppression treatment was positive for all the five patients as it led to improvements in their ataxia and enteropathy.

Furthermore, there are theories suggesting that, in some cases of ataxia, cerebellum can be affected due to low levels of vitamin E (20). This hypothesis is supported by the effective treatment observed in certain patients with CD and ataxia who received vitamin E supplements (20).

Gluten neuropathy treatment

There have been reports suggesting that following a GFD can have a positive impact on neuropathy (15). In a study involving 60 patients with GN of both the axonal type (43 patients) and sensory ganglionopathy (16 patients), it was found that strict adherence to a GFD reduced the odds of peripheral neuropathic pain by 88.7% (41). Another study followed 35 patients with gluten neuropathy, where 25 patients adhered strictly to a GFD, whereas the remaining 10 patients served as controls (28). After one year, 16 out of the 25 patients on a GFD reported an improvement in their symptoms, while none of the 10 control group patients noted any improvement.

IVIG could be also beneficial when used as a treatment alongside a GFD for individuals experiencing neuropathic pain associated with gluten-related small fiber neuropathy (SFN) (2 patients) and GN (1 patient) with concomitant GA (53). In cases of CD accompanied by multifocal axonal polyneuropathy, the administration of IVIG might be also beneficial (54). However, there have been no documented reports or controlled trials investigating the use of IVIG as a therapy for GN. Consequently, the therapeutic effectiveness of IVIG in treating GN still remains uncertain.

Deficiencies in such vitamins as B6, B12, folate and such minerals as copper resulting from malabsorption could potentially be causes of neuropathy (55). While nutritional deficiencies are rarely the sole cause of neurological symptoms, it is important to consider and investigate them since they can be easily remedied.

A deficiency in vitamin E can lead to sensory neuropathy characterized by a loss of joint position sense and head tremor. These symptoms may show some improvement with vitamin E supplementation (56).

Epilepsy treatment

Following a GFD, particularly when the issue developed soon after the onset of epilepsy, has proven to be beneficial in controlling seizures (32). In a systematic review of 70 patients, 44 of these experienced a lowering of seizure frequency, normalization of EEG patterns and ASM dose reduction after implementing a GFD (57). Another prospective study showed seizure control and discontinuation

of ASM in 6 out of 7 patients after five months on a GFD (58). However, some patients may require both GFD and AEDs to sustain remission of epilepsy (59). The potential mechanisms involved include reduced inflammation, which leads to a better gut function, as this enhances the absorption of ASMs and essential nutrients, while also minimizing the neurotoxic effects associated with consuming gluten (57). Furthermore, one study found that adopting a GFD had positive effects on the plasma levels of ASMs (60).

When it comes to patients with CEC, which is a syndrome referring to individuals with focal, medically refractory epilepsy and who have brain calcifications in the parieto-occipital region as seen on CT or MRI scans, it seems that relying solely on ASM has shown poor results with the majority of patients (73%) not responding to treatment. However, there appears to be an effective response when incorporating a GFD as 53% of patients managed with GFD have shown some improvement (45).

In the case of patients with lobe epilepsy and HS, the likelihood of seizure control after starting a GFD seems to be influenced by two factors; the duration of epilepsy prior to starting a GFD and the age at which they undertook the diet (29). The chances of success tend to decrease with the duration of epilepsy before initiating a GFD and with advancing age. Therefore, for individuals with temporal lobe epilepsy, it is advisable to start a GFD early for optimal effectiveness. Some authors speculate that those who have had epilepsy for a long period of time and already have established HS are less likely to benefit from GFD treatment (29).

Regrettably, there have been cases where patients have tried both GFD and ASM, but they still experience seizures. In these situations, surgical resection may be recommended for intractable seizures, localized in either occipital or temporal lobes (61). There are four cases where surgical resection was performed, specifically, on cerebral calcifications, in an attempt to resolve intractable seizures (46). Out of these cases, one patient did not opt for surgery, two patients were responsive to surgery, and one patient responded well to a combination of surgical resection and GFD.

Gluten encephalopathy treatment

Gluten encephalopathy encompasses a range of clinical manifestations ranging from occasional headaches which improve with a GFD to severe and debilitating headaches, accompanied by focal neurologic deficits and abnormal white matter on MRI scans that persist even after adopting a GFD. While the white matter abnormalities may not completely disappear with adhering to a GFD, such a diet can halt the progression of MRI changes and lead to the resolution of cognitive difficulties and headaches (18). A significant majority (80%) of individuals with CD and headache reported an improvement or complete relief after strictly following a GFD for one year (95). A systematic review on headaches in patients with CD also found similar levels of improvement (75%) (62). Furthermore, in pediatric patients with CD adopting a GFD, this treatment resulted in headache resolution in up to 71.3% of the investigated cases (49).

In addition to direct clinical improvement, studies have shown that adhering to a GFD can normalize cortical hypoperfusion abnormalities observed in SPECT scans (50). Although white matter abnormalities and brain calcifications are irreversible, once patients with CD strictly adhere to a GFD, a lower incidence of white matter abnormalities is observed (50).

What does the future hold for additional treatment options?

Currently, there are several non-dietary therapies (NDT) in clinical trials. The NDTs of the current interest include tight junction integrity (larazotide acetate) (63); oral enzyme supplements (latiguluinase) (64); TG2 inhibition (65); and induction of gluten tolerance with *Nexvax2* vaccine (66). Larazo-

tide acetate (LA), previously known as AT 1001, is an octapeptide derived structurally from the zonula occludens toxin produced by Vibrio cholerae (67). It acts as an inhibitor of the zonulin receptor, which helps to reduce the permeability of the intestinal barrier in and around tight junctions. Clinical trials involving LA have demonstrated its effectiveness not only in reducing gastrointestinal symptoms, but also in alleviating headaches and fatigue (68). However, further research is needed to determine its impact on reducing the risk of other neurological manifestations. **Oral enzyme** therapies are showing promise as an alternative treatment for CD. Glutenases, gluten-degrading enzymes that are proline & glutamine-specific endoproteases, could be particularly beneficial in ameliorating the effects caused by accidental gluten ingestion (64). One extensively studied enzyme is Latiguluinase or ALV003 which is a protease that targets gluten. A post hoc analysis revealed that patients who were seropositive and received the highest dose of ALV003 experienced symptomatic improvements in bloating and fatigue (69). As mentioned above, **transglutaminase** has been identified as a pivotal factor in the development of CD. Hence, inhibiting transglutaminase 2 (TG 2) could potentially prevent the presentation of peptides by HLA DQ2/DQ8 and decrease the proliferative response of gluten-reactive T cells. Mercaptamine, or cystamine, is the only other commercially available TG2 inhibitor, but the therapeutic role in CD has not been thoroughly studied (70). Developments are currently underway in **immunotherapy** techniques aimed at reducing the inflammatory reaction caused by gluten consumption in patients with CD. The objective goal of immunotherapeutic treatments is to achieve complete tolerance to ingested gluten by targeting CD4+ T cells in the intestines and rendering them inactive when exposed to gluten (71). By decreasing the inflammatory reaction, such as the production of IFN γ, it may be possible to treat or prevent neurological manifestations associated with CD. **Riluzole, Troriluzole, CAD-1883** and **TAK-831 Riluzole** act by promoting the opening of a small-conductance calcium-activated potassium channel opener and enhancing glutamate transporters. This ultimately helps improve the functioning of Purkinje cells (55). The promotion and enhancement of these mechanisms work together to reduce over-firing in Purkinje cell fibers, thereby alleviating the symptoms of ataxia. However, it remains unclear whether these drugs can provide benefits for patients experiencing recurring gluten ataxia while strictly adhering to a GFD (55).

Conclusion

In summary, the clinical significance of this article was to cover the various neurological manifestations of CD, such as gluten ataxia, gluten neuropathy, gluten encephalopathy, and epilepsy. These conditions are strongly associated with a lower quality of life and a higher rate of hospitalization. It is fairly challenging for a physician to diagnose CD when a patient presents with neurological symptoms. Thus, it is imperative for clinicians to diagnose these conditions at an early stage to prevent patients from unnecessary suffering. In GA, the main diagnostic tools should be a serological marker of anti-TG6 antibodies and MRS; in GN, anti-ganglioside, anti-TG6 antibodies should be screened alongside sural nerve biopsy and sudoscan; MRI and EEG are the cornerstone in diagnosing epilepsy; In GE, to detect WMA and altered cerebral blood flow, MRI with SPECT should be used. Nonetheless, the correct treatment approach is also important, especially if the current neurological disease progresses and may cause a permanent disability. Treatment should include symptomatic management; however, the hallmark in gluten-related neurological manifestations is embarking on a strict GFD as soon as possible. In the majority of such diseases, with the exemption of cortical myoclonus and advanced dementia, GFD has a positive therapeutic effect. Immunosuppression is only used in cases where strict GFD alone has not been beneficial and in those patients who manifest refractory CD.

We believe that this article can help inform practicing physicians and spread awareness with regard to the neurological features, diagnosis and treatment of CD.

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