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BEYOND THE GUT: EXPLORING NEUROLOGICAL IMPLICATIONS OF CELIAC DISEASE

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ABSTRACT

Introduction and purpose: The aim of this article is to provide a comprehensive review of the neurological manifestations associated with celiac disease (CD), a systemic autoimmune disorder triggered by gluten in genetically predisposed individuals. Although CD is traditionally associated with gastrointestinal symptoms, its neurological effects are increasingly recognized and require further analysis.
Material and methods: This narrative review was conducted using literature sourced from scientific databases including PubMed, Scopus, Web of Science, and Google Scholar.
State of knowledge: Neurological symptoms in CD, such as cerebellar ataxia, peripheral neuropathy, cognitive impairment, seizures, and"brain fog, " may precede or occur without gastrointestinal symptoms. Diagnostic strategies include genetic and serological testing, neuroimaging, and neurological assessments. Although a gluten-free diet remains the cornerstone of therapy, additional treatments such as vitamin E supplementation and intravenous immunoglobulin have shown promise in specific cases.
Results: Neurological symptoms affect a significant proportion of patients with celiac disease, and early diagnosis combined with strict adherence to a gluten-free diet improves treatment outcomes. Quality of life and mental well-being also improve, which is particularly noticeable in the first year of treatment. Celiac disease is characterized by a diverse spectrum of neurological symptoms that may remain undiagnosed without a multidisciplinary approach.

KEYWORDS

Celiac Disease, Neurological Manifestations, Gluten-Free Diet, Neuroimmunology, Quality of Life

CITATION

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Introduction

This article was created with the aim of providing a comprehensive overview of the neurological aspects of celiac disease (CD). Following chapters will discuss the etiology, focusing on the genetic and environmental factors contributing to celiac disease. The article will highlight the wide range of gastrointestinal and extra-intestinal symptoms, including neurological manifestations such as cerebellar ataxia, peripheral neuropathy, and cognitive impairment. The mechanis JMJms of neurological injury, including immunological and nutritional factors, will be explored. Diagnostic approaches, combining genetic, serological, and imaging techniques, will be reviewed. The article will address the management and treatment of CD, emphasizing the importance of a gluten-free diet and potential supplementary therapies for neurological symptoms. Finally, we will look at the everyday lives of patients, focusing on their quality of life in relation to their illness.

Current state of knowledge:

1. Etiology

Celiac disease (CD) is an autoimmune disorder precipitated by the ingestion of gluten in genetically predisposed individuals, leading to damage to the small intestine and subsequent malabsorption. The prevalence of CD in the general population ranges from 0.3% to 1.5% [1]. Clinically, while diarrhea and gastrointestinal symptoms are common at the onset or early stages of the disease, their frequency has decreased compared to the past. It is widely recognized that the classic gastrointestinal presentation of CD constitutes only a small fraction of the broader "CD iceberg," with more than 50% of adults demonstrating significant extra-intestinal manifestations, even in the absence of typical gastrointestinal symptoms [2]. Consequently, CD is regarded as a complex systemic disorder with a multifactorial pathogenesis, resulting from environmental gluten exposure in genetically susceptible individuals.[1]

2. Neurological symptoms

Neurological manifestations in celiac disease (CD) can occur at any point during the disease course, potentially presenting before, concurrently, or after the classical gastrointestinal symptoms and signs. Neurological symptoms may also be the sole manifestation of CD in some cases. On the neurological spectrum, CD may manifest as cerebellar ataxia, peripheral neuropathy, seizures, headaches, cognitive impairment, and various neuropsychiatric disorders [3]. The prevalence of neurological involvement in CD is substantial. A recent prospective study suggests that up to 40% of patients newly diagnosed with CD exhibit some form of neurological illness. This conclusion is based on comprehensive assessments that include patient history, expert neurological examination, magnetic resonance spectroscopy, and supportive serological findings, underlining the significant neurologic impact of this systemic autoimmune disorder [1].

3. Gluten ataxia

Hadjivassiliou et al. coined the term “gluten ataxia” to describe the concomitant presence of sporadic idiopathic ataxia and a high prevalence of AGA in the serum. The prevalence of gluten ataxia is about 20–45% (20% when considering all individuals with ataxias, 25% in individuals with sporadic ataxias, and 45% in individuals with idiopathic sporadic ataxias) while the prevalence among AGA-positive patients was 10% in genetically-confirmed ataxias, 10–18% in not genetically-confirmed familial ataxias, and 12% in healthy individuals. The higher prevalence of AGA among idiopathic sporadic ataxias was also confirmed in smaller studies [4]. Gluten ataxia usually has an insidious onset, with a mean age of presentation of approximately 50 years. Of note, less than 10% of patients with gluten ataxia have gastrointestinal symptoms, although a third show evidence of enteropathy on histology [1]. Gluten ataxia usually presents with pure cerebellar ataxia or, rarely, with ataxia in combination with myoclonus, palatal tremor, opsoclonus, or chorea. In addition, up to 80% of cases of gaze-evoked nystagmus and other visual signs of cerebellar dysfunction have been described, as well as approximately 60% of individuals with combined neurophysiological signs of sensorimotor and axonal neuropathy [1].

4. Mechanism of neurological injury in gluten ataxia

The mechanisms underlying neurological injury in gluten ataxia (GA) remain incompletely understood, partly because the neurological manifestations in celiac disease itself are multifaceted, arising from a confluence of nutritional deficiencies, immunological injuries, toxic insults, and metabolic disturbances [5]. Immunologically mediated injury is a recognized pathogenic process in the nervous system, particularly in cerebellar ataxia (CA)[2]. From the intestinal perspective, the pathways of immunological injury are relatively well-defined, initiated by antigen-antibody interactions. It is hypothesized that in the context of HLA (DQ2/8) genotypes, gluten acts as an antigen that is presented to pre-sensitized α/β receptor-bearing T lymphocytes [6]. This interaction triggers a cascade of immunological events, including the production of cytokines through both humoral and cellular immune responses, leading to mucosal pathology as described by Marsh and colleagues. A possible explanation for this response is the loss of immune tolerance and an immunological reaction targeting primary autoantigens such as tissue transglutaminase (tTG), a family comprising nine related enzymes in humans involved in the post-translational modification of proteins [1]. In the small intestine, tTG, particularly tTG-2, is responsible for enzymatic reactions that include cross-linking, amine formation, and deamination, processes essential for cell adhesion, signal transduction, and apoptosis. tTG-2 is specifically implicated as the primary target in the intestinal epithelium in the gastrointestinal manifestations of CD. Conversely, tTG-3 is thought to be involved in dermatitis herpetiformis, a skin condition associated with CD. However, the immunopathological mechanisms by which gluten may induce neurological damage in the central nervous system (CNS) remain a subject of considerable debate and ongoing research [1].

5. Diagnosis

The diagnosis of celiac disease involves a combination of genetic testing, serological tests, histological examination, and various imaging and clinical assessments to identify both intestinal and extra-intestinal manifestations [1]. For the intestine, genetic testing for HLA-DQ2 and HLA-DQ8 is fundamental. The gold standard diagnostic procedure is a duodenal biopsy. To assess the intestinal barrier, genetic testing for HLA-DQ2 and HLA-DQ8 is again employed, supplemented by duodenal biopsy and intestinal barrier leakage tests. In the blood, genetic testing for HLA-DQ2 and HLA-DQ8 is crucial [7]. Serological tests for anti-gliadin antibodies, anti-endomysium antibodies, and anti-transglutaminase antibodies (Anti-TG2 and Anti-TG6) are performed to confirm the diagnosis. Evaluation of the blood-brain barrier involves testing for autoantibodies

to the gliadin-transglutaminase (TG) complex [1]. For the brain, diagnostic indicators include epileptiform changes, cortical excitability, and white matter lesions. These can be detected using various brain imaging tools such as EEG, magnetic resonance spectroscopy, diffusion tensor imaging, transcranial magnetic stimulation, and VEPs [2]. Cerebellar involvement is assessed through clinical evaluation of motor dysfunction. Non-cerebellar manifestations are shown through cognitive tests and neuropsychological assessments are essential to evaluate the cognitive and psychological impact of the disease [2].

6. Treatment

A gluten-free diet typically leads to significant improvement in gastrointestinal symptoms, normalization of antibody levels, and amelioration of histopathological changes in the small bowel mucosa. However, complete histopathological normalization is not always achieved. It is essential for patients to consult with a nutritionist for education and guidance on adhering to a gluten-free diet [8].

Neurological manifestations of celiac disease also generally improve with a gluten-free diet alone. In patients with celiac-associated ataxia, supplementation with vitamin E has shown apparent benefits [9]. Recent studies indicate that intravenous immunoglobulin (IVIG) therapy is an effective treatment for celiac-associated ataxia and may also be beneficial for treating multifocal axonal polyneuropathy in celiac patients. For epilepsy, a gluten-free diet, especially when initiated soon after seizure onset, has been useful in controlling seizures. Additionally, in cases of myoclonus syndrome where anticonvulsant or benzodiazepine therapy is not fully effective, improvement has been observed following the adoption of a gluten-free diet [8].

7. Quality of life and daily functioning of patients

One of the available prospective studies assessed changes in quality of life (QoL), anxiety, and depression in adult patients with newly diagnosed celiac disease within two years of starting a gluten-free diet (GFD). The study did not analyze typical neurological symptoms such as neuropathy or ataxia, but focused on psychological symptoms: anxiety and depression, which can be considered part of the spectrum of neurological symptoms of celiac disease. The results highlighted a significant improvement in quality of life and psychological well-being, especially in patients who strictly adhered to the diet. The greatest benefits were observed during the first year after diagnosis. This improvement persisted for two years, highlighting the lasting positive impact of adhering to the diet [10]. Yelland (2017) discusses the phenomenon of gluten-induced cognitive impairment, commonly referred to as “brain fog,” in patients with celiac disease. Symptoms such as difficulty concentrating, memory loss, and slowed cognitive processes are highlighted, and their impact on patients' daily functioning is demonstrated. The authors emphasize that such neurocognitive disorders often persist in untreated celiac disease, but also tend to improve after strict adherence to a gluten-free diet, confirming the role of immune mechanisms and possible nutritional deficiencies in their pathogenesis. This correlates with a growing body of evidence indicating that neurological symptoms (including the aforementioned cognitive impairments) may precede gastrointestinal symptoms or occur independently of them [5]. These observations reinforce the need for comprehensive diagnostic strategies outlined in this paper, as neurocognitive symptoms may occur independently of gastrointestinal manifestations, highlighting the systemic nature of celiac disease.

8. Research gaps and future prospects

Although significant progress has been made in understanding the neurological side of celiac disease, still several important gaps remain. Current research has not fully elucidated the immunopathogenic mechanisms underlying selective neural tissue damage, particularly the role of anti-transglutaminase 6 (TG6) antibodies and their correlation with clinical outcomes [11]. Additionally, while neuroimaging and biomarker studies show promise, there is still a lack of standardized diagnostic protocols to identify patients at risk of gluten-related neurological injury [12]. Evidence on the long-term effectiveness of adjunctive therapies, such as immunomodulation and neurorehabilitation, beyond a strict gluten-free diet is limited, necessitating controlled clinical trials to explore these interventions [13]. Future research should prioritize multicenter, longitudinal studies combining advanced neuroimaging techniques, biomarker profiling, and genetic analysis to develop predictive models and personalized treatment strategies. Furthermore, in order to take into account the systemic and multifactorial nature of CD and improve patient outcomes, it will be necessary to adopt an interdisciplinary approach, encompassing a range of fields such as gastroenterology, neurology, dietetics, and psychology.

Conclusions

The neurological symptoms of celiac disease pose a serious clinical challenge due to their variability and frequent occurrence without gastrointestinal symptoms. Reports indicate that conditions such as cerebellar ataxia, peripheral neuropathy, and cognitive impairment may precede intestinal symptoms, highlighting the systemic nature of CD. Early diagnosis supported by a combination of genetic, serological, and neuroimaging techniques is essential for preventing neurological damage. A strict gluten-free diet remains the basis of treatment, but in specific cases, adjunctive therapies, including vitamin supplementation and immunomodulatory approaches, may provide additional benefits. In the coming years, research should focus on elucidating immunopathogenic mechanisms, validating new biomarkers, and developing standard protocols to improve the detection and treatment of neurological complications in celiac disease.

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