*International Journal of Celiac Disease, 2019, Vol. 7, No. 1, 16-20*
Available online at http://pubs.sciepub.com/ijcd/7/1/8
Published by Science and Education Publishing
DOI:10.12691/ijcd-7-1-8

# Neurological Complications of Coeliac Disease

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*Received January 10, 2019; Revised February 21, 2019; Accepted March 08, 2019*

**Abstract** Coeliac disease (CD) is a chronic autoimmune enteropathy of the small intestine that occurs in genetically predisposed individuals. It is characterized by atrophy of intestinal villi accompanied by an increase in the number of intraepithelial lymphocytes and crypt hypertrophy as well as the presence of specific endomysial antibodies (EMA), IgA tissue transglutaminase antibodies (IgA-tTG), and IgA and IgG deaminated gliadin peptide antibodies (DGP IgA and IgG). CD is associated with a wide spectrum of clinical signs and symptoms secondary to malabsorption (vitamin deficiency, anaemia, osteoporosis) or unrelated to the gastrointestinal tract. Neurological disorders are a common problem in patients with CD and are not always accompanied by gastrointestinal symptoms. The most common neurological manifestations of CD are cerebellar ataxia, epilepsy, and peripheral neuropathy.

***Keywords:*** *coeliac disease, gluten ataxia, neuropathy, gluten*

**Cite This Article:** Justyna Chojdak-Łukasiewicz, Edyta Dziadkowiak, Małgorzata Błauciak, and Bogusław Paradowski, "Neurological Complications of Coeliac Disease." *International Journal of Celiac Disease*, vol. 7, no. 1 (2019): 16-20. doi: 10.12691/ijcd-7-1-8.

## 1. Introduction

Coeliac disease (CD) is a chronic inflammatory autoimmune disease of the small intestine caused by persistent gluten intolerance, which affects genetically predisposed individuals [1]. It has been known since ancient times. The name comes from the Greek word 'koiliakos', meaning 'suffering in the bowels'. In the late first/early second centuries, doctor Aretaeus of Cappadocia described for the first time a malnutrition syndrome associated with chronic diarrhoea. In the nineteenth century, information appeared about the possibilities of elimination of starch from some grain products in people with symptoms of enteropathy [2,3]. In 1952, it was shown that the factor responsible for CD symptoms was gluten [3]. The classical form of CD with dominant gastrointestinal symptoms in the form of the malabsorption syndrome was described by Danish paediatrician Wilhelm Dickie in 1953 [4].

CD affects about 1% of the population. The incidence in Europe varies from 1: 100 to 1: 300 individuals [1,2,5,6]. The disease is slightly more common in western Ireland, Sweden, and Finland [7,8,9]. The differences in the geographical prevalence of the disease may be due to environmental factors. Women are affected twice as often as men. The disease usually begins in early childhood but can develop at any age. About 60% of cases concern adults, with a peak incidence in the 3rd and 4th decades of life [10].

CD is associated with other autoimmune diseases. There are a number of patient groups where the risk of developing CD is higher compared to the general population. Due to a genetic predisposition, the relatives of the patient are more susceptible to CD development. A first-degree relationship is associated with about 10% risk of the disease while in a second-degree relationship it varies from about 3 to 4% [11]. About 100 diseases can be associated with malabsorption of gluten. In particular, it significantly corelates with type 1 diabetes (frequency around 5-8%), thyroid dysfunctions (Hashimoto's thyroiditis, Graves' disease), systemic connective tissue diseases (mainly Sjögren syndrome), biliary cirrhosis, and IgA deficiency [2,12]. One of the risk groups are patients with chromosomal aberrations: Down, Williams, and Turner syndromes [13].

The classical malabsorption syndrome, for years regarded as the only form of CD, is rarely seen. The clinical picture of CD is very diverse, consisting mainly of atypical forms. According to estimates, for every case of classical CD there are 3-7 atypical cases [14]. Epidemiologically, CD is presented as an iceberg, the tip of which consists of fully symptomatic forms, while the underwater part is made up of asymptomatic and atypical forms. The skin form of CD is Duhring's disease (dermatitis herpetiformis), which in 10% of the patients coexists with gastrointestinal symptoms. There are multiform itchy skin changes ranging from erythematous outbreaks to blisters and papules with numerous scars and discolourations. Based on the nature of the symptoms and changes in the mucosa of the small intestine, we can distinguish four types of CD: classical, atypical, silent, and latent. In the classical form, which usually manifests up to the age of 4, gastrointestinal symptoms predominate, such as steatorrhoea, weight loss, lack of appetite, flatulence, and widening of the abdominal girth as well as oedema, behavioural disorders, and regression of psychomotor development. In the atypical form, symptoms from the gastrointestinal track may be less

pronounced, while symptoms from other systems and organs dominate. The clinically silent and latent forms are often asymptomatic. In the latent form, specific antibodies are found in the serum, whereas the clinically silent form is characterized by the presence of asymptomatic atrophy of intestinal villi [1,2,15,16].

## 2. Aetiology

According to Köttgen, the occurrence of the disease is determined by genetic, environmental, infectious, immunological, and metabolic factors [17,18]. People carrying HLA-DQ2 and/or HLA-DQ8 haplotypes are predisposed to the disease.

The main cause is intolerance to gluten, which is a protein found in wheat, rye, barley, spelt, and triticale. In genetically predisposed individuals, exposure to gluten causes a reaction of the immune system, resulting in damage to the mucosa of the small intestine with destruction of villi, proliferation of intraepithelial lymphocytes, and intestinal crypt hypertrophy [15].

The mechanism leading to neurological disorders in CD is not completely understood. It is assumed that the major role is played by abnormal immune response that manifests itself under the influence of gluten. Deficiencies of vitamins and trace elements, secondary to malabsorption, are also important. In cerebellar ataxia and peripheral neuropathy, a mechanism of humoral response has been proposed based on cross-reaction of gliadin antibodies with Purkinje cells [19,20,21]. The psychiatric symptoms accompanying CD may result from the coexistence of deficiencies of B vitamins and tryptophan. Patients with depression and CD show reduced levels of monoamines in the serum and cerebrospinal fluid (CSF). In 10-15% of patients with psychiatric disorders, folacin levels are reduced [22].

## 3. Neurological Symptoms

Neurological symptoms are the most common parenteral manifestation of CD, affecting 8-22% of adult patients, while occurring slightly less frequently in children [23,24]. The involvement of the nervous system in CD has been known since the beginning of last century. In 1905, Brown described two patients with concomitant neuropathy. In 1996, Smith and Cook described 16 patients with neurological symptoms and CD confirmed by intestinal biopsy. The most common symptoms were gait disturbances and polyneuropathy [25]. Neurological complications in CD are characterized by a broad clinical spectrum. Symptoms of central and peripheral nervous system involvement may occur much more frequently, even in the absence of gastrointestinal symptoms [26,27,28,29]. A study by Hadjivassiliou et al. found the presence of gliadin antibodies in 57% of the patients with neurological symptoms of unknown aetiology [30].

The best-known neurological complication is gluten ataxia, which occurs in 2.7-5.4 % of patients with CD and may occur regardless of gastrointestinal symptoms [31,32,33]. One-third of patients with symptoms of ataxia have features of enteropathy, and less than 10% of patients have gastrointestinal symptoms. Studies by various authors indicate that up to 16% of people with symptoms of ataxia of unknown aetiology often show changes in intestinal biopsy [30,34,35,36]. The term ‘gluten ataxia’ was first used by Hadjivassiliou in 1998 to describe patients with cerebellar symptoms with accompanying gliadin antibodies [37]. Neuroimaging tests show features of cerebellar atrophy, while neuropathological examination reveals loss of Purkinje cells and atrophy of the posterior horns of the spinal cord [38-41]. Patients with gluten ataxia show typical HLA-DQB1 haplotype, antibodies to cerebellar Purkinje cells, elevated IP-10 chemokine level, and presence of oligoclonal bands in the CSF [38,39,40,41,42].

The second most frequent neurological manifestation of CD is peripheral neuropathy (in 43% of adults and in 7.4% of children) [43]. The clinical picture is diverse, ranging from pure motor neuropathy, to multiple mononeuropathy, autonomic neuropathy, or Guillain-Barré syndrome. The changes can be axonal or demyelinating. The most common is small fibre neuropathy [44,45,46,47]. Symptoms of neuropathy can occur regardless of gastrointestinal symptoms. In patients with CD, the risk of peripheral neuropathy is 2.5 times higher than in general population [43,48,49]. CD has also been confirmed in 8% of patients with clinical symptoms of neuropathy and normal electrophysiological outcomes. People with neuropathy are found to have antiganglioside antibodies (anti-GM1, GMD, GD1a, GD16) [50].

There is also a well-documented relationship between epilepsy, occipital calcifications, and CD [51,52]. The relationship between epileptic seizures and CD was described for the first time by Visakorpi in 1970 [53]. CD is associated with twice the risk of epileptic seizures compared to the general population, while 0.8-6% [51,54] of patients with epilepsy are diagnosed with CD. No similar relationship was found in children. In most cases, focal seizures are observed in the temporal or occipital lobes due to the presence of calcifications in these areas [56]. The calcifications are similar to those of Sturge-Weber disease and consist of vessels, fibrotic veins, and jagged microcalcifications.

There are no conclusive data linking headaches with CD. Gabrielii et al. reported tenfold higher prevalence of migraine headaches (4.4% in CD versus 0.4% in the control group) [57]. Different results were obtained by Nikipour et al., who found no significant difference in comparison to the general population [58]. Cicarelii et al. reported a significantly higher incidence of headaches (migraine and/or tension-type) in patients with CD (46%) compared to the control group (29%). In children with CD, headaches are slightly more common [58,59]. Some patients with chronic migraine show an improvement after using a gluten-free diet despite the lack of diagnosis of CD.

A large group of patients experience problems with memory and concentration in the form of mild cognitive impairment. The symptoms are referred to as ‘brain fog’ [60]. Some patients may develop dementia with profound cognitive impairment [61,62,63].

As many as one-third of CD patients have depressive disorders and other psychiatric symptoms (anxiety disorders, excessive excitability, bipolar disorder, schizophrenia) [64]. Other, less common neurological

manifestations include myopathy, myelopathy, encephalopathy, and stiff-person syndrome. There have been occasional cases of chorea, polymyositis, and venous thrombosis in the course of CD. Idiopathic intracranial hypertension may be related to CD [65,66,67].

## 4. Diagnosis

Diagnosis of the disease in adults is based on the guidelines of gastroenterological societies (American College of Gastroenterology, British Society of Gastroenterology, and World Gastroenterology Organization). The diagnosis of CD uses serological tests, evaluation of small intestine biopsies, and genetic tests [1,2,68]. For diagnosis in adults, it is necessary to demonstrate the presence of antibodies specific for this disease and typical changes in the small intestine mucosa. In the case of suspected CD in children, small intestine biopsy may be omitted. Guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) attribute primary importance to serological and genetic tests [68]. Specific antibodies are found in the serum of 40-90% of the patients. At present, serological diagnosis uses three types of antibodies:

- IgA and IgG gliadin antibodies, which are characterized by high specificity;
- IgA and IgG endomysial antibodies with high specificity and sensitivity;
- Tissue transglutaminase antibodies (tTG) with the lowest specificity; they may be present in other autoimmune diseases (psoriasis, Crohn's disease, myocardial damage) [69,70].

A key role in diagnosis is played by biopsy of the small intestine mucosa with changes typical of CD in the form of atrophy of intestinal villi (partial, almost complete, and complete atrophy), intestinal crypt hypertrophy, and an increase in the number of intraepithelial lymphocytes (over 25 per 100 epithelial cells). The histological evaluation of the intestine uses the three-stage modified Marsh-Oberhuber classification (stage 0: normal picture of the intestinal mucosa, stage III: atrophic changes typical of classical CD) [71].

The diagnosis also uses determination of specific haplotypes in the HLA DQ2 system and, less frequently, in the DQ8 system. About 90% of CD patients are carriers of the DQ2 molecule, encoded by DQA1*05 and DQB1*02 alleles. The remaining 5-10% of patients carry the DQ8 molecule, encoded by DQA1*03 and DQB1*03 alleles. The HLA test is useful in people with uncertain diagnosis of CD, in the case of minor histopathological changes and negative serological tests.

Genetic tests can also be useful in isolating clinically asymptomatic people in risk groups who need further diagnosis.

## 5. Treatment

Early detection of CD and introduction of a diet is crucial. Unrecognised CD leads to many complications and is associated with metabolic bone disorders (osteomalacia, osteoporosis) and deficiencies of vitamins and minerals. It was demonstrated that untreated CD correlated with development of gastrointestinal cancers, mainly adenocarcinomas and small intestinal lymphomas. Patients have a higher risk of developing atherosclerosis and cardiovascular events [72,73].

After the introduction of a diet, clinical improvement is quickly achieved in the form of reduced gastrointestinal symptoms, whereas regression of lesions in the intestinal mucosa and normalisation of specific antibodies take somewhat longer.

A gluten-free diet consists in total and continuous elimination of dietary wheat, oats, rye and barley. In addition, an important role is played by supplementation of vitamin and mineral deficiencies. Consuming even small amounts of gluten causes a recurrence of symptoms and risk of complications. A gluten-free diet supports antiepileptic treatment, reduces the frequency of migraine attacks, and exerts a beneficial effect on the symptoms of cerebellar ataxia [74,75,76,77]. Litchwark and Yelland also noted a beneficial effect on cognitive functions [61]. In the case of psychiatric symptoms, the impact of a gluten-free diet is ambiguous. Elimination of dietary gluten reportedly improved mood and alleviated depressive symptoms, but it was also reported that the diet had no impact on psychiatric symptoms. Addolovato et al. showed a positive effect of diet on remission of anxiety symptoms but they did not observe stabilisation of depressive symptoms [22].

## 6. Conclusion

CD is an enteropathy of the small intestine, which is associated with a number of clinical symptoms.

Diverse clinical picture may delay correct diagnosis. CD can present exclusively with neurological symptoms. In the case of neuropathy and cerebellar symptoms with unclear aetiology or other syndromes, it is necessary to exclude CD. A gliadin antibody test should be included in the set of auxiliary tests at neurological departments.

## Acknowledgments

None.

## Disclosure Statement

I declare that all the authors of the manuscript "Neurological complications of coeliac disease" have not got any financial agreement with any organization and other financial relationships (stock ownership in medically-related fields, intellectual property rights, consultancies, advisory boards, expert testimony, employment partnerships contracts, honoraria, royalties grants and other) in the three past years, related and unrelated to the current research.

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