The Connection Between Celiac Disease and Nervous System and Mental Disorders

Związek choroby trzewnej z chorobami układu nerwowego i zaburzeniami psychicznymi

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Abstract

Celiac disease (CD) is a complex autoimmune enteropathy that affects the small bowel after gluten ingestion in genetically predisposed patients. It is well known that CD may be associated with various neurological manifestations. Celiac disease in adolescents is associated with an increased risk of mental and neurological disorders, especially when there was no diagnosis and treatment of CD in childhood. In most cases these disorders precede the diagnosis of CD and in many cases the symptoms appear to improve after starting a gluten-free diet. Although clinical findings appear to be consistent with a connection between these diseases, the mechanisms involved are unclear and need to be studied further (Adv Clin Exp Med 2008, 17, 5, 495–502).

Key words: celiac disease, nervous system diseases, mental disorders.

Celiac disease (CD) is defined as a chronic autoimmune enteropathy resulting from sensitivity to gluten. The disease affects the small intestine and leads to lesion or even massive loss of absorptive villi. Gluten refers to a group of proteins which are present in the four basic cereals and have different levels of toxicity. These proteins are gliadins (wheat), avenins (oat), secalins (rye), and hordeins (barley). CD is one of the most common genetic disorders, its prevalence being approximately 1% in the general population, and it is associated with HLA-DR3, DQ2, and DQ8 haplotypes. It mainly affects whites and is only rarely described in Africans or Chinese. The reasons for this are both rare diagnosis due to inferior diagnostic possibilities and a different type of diet from that of European countries, where CD is most commonly diagnosed [1–3]. Epidemiological studies show two main periods connected with the highest risk of developing the disease, the first at the age of 5 years and the second in the fourth and fifth decades of life. Although CD may be diag-
nosed at any age, the age at which it is diagnosed is connected not only with genetic predisposition, but also with many environmental factors, diet, coexisting diseases, as well as diagnostic possibilities and the level of doctors’ knowledge about the disease [4, 5].

Gluten in genetically predisposed individuals can cause changes typical of CD. Several studies suggest that the toxicity of gluten may be dependent on the dose, the kind (avenine is the least toxic), the age when gluten is introduced in the diet, and the patient’s individual sensitivity. The coexistence of some environmental factors, such as bacterial overgrowth and antibiotics, also has negative influence and may uncover formerly asymptomatic cases of the disease [4, 6, 7].

The tactics of introducing gluten-containing food into the diet prevailing in most countries cause changes in the clinical presentation of the disease.

Among adolescents there are four forms of CD: 1. Classic form – this is the typical constellation of symptoms, with malabsorption syndrome and chronic diarrhea. Both serological tests and biopsy results are positive. This occurs less often nowadays because of recent changes in diet. 2. Atypical form – intestinal symptoms are poor and extraintestinal symptoms are mainly present. Characteristic are positive endomysial antibodies in the serum and lack of villi in biopsy specimens. 3. Silent form – there are no clinical manifestations, but serological tests are positive and a lack of villi is observed. Latent form – there are no clinical symptoms, the small intestinal mucosa is normal, but characteristic antibodies are present. With the appearance of some additional factor, such as infection, pregnancy, or chronic distress, there is a possibility of transformation to the typical form of the disease.

For many years, atypical or silent forms of the disease with extraintestinal symptoms have been observed in adults [8–10]. There is an evident connection between CD and mental disorders. Hadjivassiliou, Grunewald, and Davies-Jones studied the frequency of antigliadin antibodies in patients with various neurological disorders compared with a group of healthy volunteers. Antigliadin antibodies were present in 57% of the patients with neurological disorders of unknown etiology, in 5% of patients with neurological disorders with a diagnosed cause, and in 12% of the persons in the control group. In neurological patients with gluten sensitivity, HLA DQ2 antigens were present in 70% and HLA DQ8 in 9% [11].

There are two theories that may explain the presence of neurological symptoms in CD. The first says that these symptoms are a consequence of malabsorption syndrome and a secondary lack of vitamins (B₁₂, B₆, E, D, folic acid). This theory does not explain the problem for two reasons. First, a lack of the B₁₂ vitamin and folic acid has been diagnosed only in some cases and their supplementation does not cure the neurological changes. The second reason is that in some patients with gluten sensitivity and neurological symptoms there is normal mucosa in the duodenum. According to the second theory, autoimmune mechanisms and antigliadin antibodies, which would directly damage the nervous system, play the main role [12, 13]. Neurological symptoms are present in 6–12% of patients diagnosed with CD, most often cerebellar ataxia and peripheral neuropathy [2, 11, 13, 14].

Peripheral Neuropathy and Neuromuscular Disorders

Hadjivassiliou, Grunewald, and Davies-Jones studied a group of 101 of patients with idiopathic peripheral neuropathy, with confirmed gluten sensitivity in 40% of the cases. The most common type of neuropathy was sensorimotor axonal neuropathy, diagnosed in 26 of the patients, followed by mononeuropathy multiplex in 15 cases. Pure motor neuropathy was diagnosed in 10 patients. Less frequent were small fiber neuropathy, diagnosed in 4 patients, and mixed axonal and demyelinating neuropathy in 2 cases. Peripheral neuropathy is usually chronic and progressive [11].

Chin, Sander, Brannagan et al. screened for the presence of CD’s characteristic changes (IgG and IgA antigliadin and IgA transglutaminase antibodies) in a group of 400 patients diagnosed with peripheral neuropathy. Duodenal biopsy was performed in all patients with elevated antigliadin or transglutaminase antibody levels, with subsequent exclusion of individuals without histological features of enteropathy. CD was diagnosed in 5% of the patients (20 patients), or in 2.5% without 9 individuals who had already been diagnosed with CD in the past. In 30% of the cases (6 patients) there were no gastrointestinal symptoms; therefore, without participating in this study they probably would not have ever been diagnosed with CD. In all cases, neuropathy was manifested by burning and numbness in the hands and feet. In all 20 patients, electrophysiological studies were performed, with normal results in 90% of the cases [15].

In a study by Hadjivassiliou, Chattopadhyay, Davies Jones et al. published in the 1990s, cases were described in which celiac disease and neuromuscular disorders coexisted. There were nine patients in the described group, and the neuro-
muscular symptoms always preceded the diagnose of celiac disease. The diagnoses were based on elevated levels of antigliadin antibodies and microscopic examination (lowered duodenal villi counts). The study showed that the spectrum of neuromuscular disorders associated with celiac disease is quite broad; the authors described cases of Guillain-Barre syndrome, neuromyotony and axonal sensory and motor neuropathy, and sometimes also primary muscular lesions. They confirmed the existence of primary muscular lesions, which were secondary in some patients to inflammatory processes, allowing diagnosis of multi-muscular inflammation and, in one patient, inclusion body myositis. In these patients, signs connected with the gastrointestinal tract were absent or very mild [15]. Celiac disease can rarely be connected with stiff-man syndrome and myelopathy [11, 16, 17]. In another study by Hadjivassiliou et al. based on electrophysiological examination, axonal, sensory, and motor neuropathy coexisting with cerebellar ataxia was confirmed in 45% of the patients [18].

The possible influence of a gluten-free diet has not been yet confirmed. The diet can lessen neurological symptoms as well as have no significant influence at all [15, 19]. Luostarinen, Himanen et al. performed an extensive neurological evaluation of 26 patients focusing on symptoms of neuropathy. The patients were diagnosed with celiac disease and had been on gluten-free diets since the diagnosis was established, i.e. for an average of 3 years. They were all in remission, confirmed clinically and with microscopic examination. Nine of the patients reported paresthesia and sensory deficits in distal parts of extremities. Neurological examination showed lowered or absent tendon reflexes and sensory deficits. Electroneurography confirmed axonal neuropathy, mainly of a motor kind, in 23.1% of patients, i.e. 6 patients, only half of them being symptomatic. The authors’ conclusion was that celiac disease, even properly controlled and without absorption deficits, is connected with an elevated risk of developing neuropathy [17]. This can be a result of gluten sensitivity in contact with even small amounts of this substance, which is almost impossible to eliminate from food, as well as an effect of earlier developed peripheral nerve or dorsal nerve root lesions, which can be impossible to revert. In such cases, a gluten-free diet can only slow the process of peripheral nerve destruction [15].

Cerebellar Ataxia

Gluten-dependant ataxia is the most common cause of rare idiopathic ataxia [18]. The diagnosis of idiopathic cerebellar ataxia can be establish when the following criteria are fulfilled: the cerebellar ataxia worsens and there is no proof of a focal or non-focal character of lesions, there are no degenerative diseases in the patient’s relatives, the parents are not closely related, and genetic tests for Friedreich’s ataxia and medullo-cerebellar ataxia are negative [20]. There are no characteristic symptoms of gluten-dependant ataxia and they are typical of lesions of the cerebellum; in some patients, coexistent myoclonies are present. Of the diagnostic tests, the most important are serological. Hadjivassiliou, Grunewald, Sharrack et al. tested 268 patients with cerebellar ataxia, developed because of various causes, for the presence of antigliadine antibodies. Gluten sensitivity was confirmed in 38.6% of the patients diagnosed with rare idiopathic cerebellar ataxia, in 14% of familial ataxia patients, and in 15% of patients with multi-system atrophy, which showed the most evidence cerebellar symptoms (MSA-C). In the control group of 1200 patients, only 12% were antigliadin antibody positive. Moreover, in the patients diagnosed with gluten-dependant ataxia, typical antigens of celiac disease were found: HLA DQ2 in 72% of the patients and HLA DQ8 in 6%. The symptoms of celiac disease coexisting with ataxia were walking ataxia in 100% of patients, upper and lower extremities ataxia in 90 and 75%, respectively, eye syndromes in 84%, and dysarthria in 66%. Gastrointestinal tract-related symptoms were present only in 13% of the patients and enteropathy was confirmed by biopsy material examination in 24%. MRI examination showed cerebellum atrophy in 79% of the patients [18]. In 2001, Burk, Bosch, Muller et al. screened 104 patients diagnosed with idiopathic rare cerebellar ataxia for gluten hypersensitivity using antigliadin and antiendomysium antibody levels. In 12 of the patients (11.5%) the results were positive, indicating celiac disease. Duodenal biopsy showed enteropathy-related lesions in 2 patients, but none of them showed symptoms of vitamin deficit or any other signs of malabsorption. Neurological examination showed ataxia of stance and gait (100%), dysarthria (100%), limb ataxia (97%), and oculomotor abnormalities, consisting of gaze-evoked nystagmus (66.7%), spontaneous nystagmus (33.3%), saccade slowing (25%), and upward gaze palsy (16.7%). HLA typing revealed a strong association between ataxia with gluten sensitivity and HLA DQB1*0201 haplotype, which was confirmed in 70% of the cases. All the patients with gluten-dependent ataxia had evidence of cerebellar atrophy on MRI [20]. Pellecchia, Scala, Filla et al. studied the frequency of CD occurrence in groups of ataxic patients with...
and without definite diagnoses. Of 24 patients with idiopathic ataxia, positive antigliadin and antiendomysium antibody tests were found in 12.5% (3 patients) of cases vs. no case with a positive result in the second group of 23 patients with definite diagnoses. In the group of patients with gluten-dependent ataxia, no known anticerebellar antibodies were found, which may suggest the neurotoxic action of antigliadin antibodies. In all the studied patients with CD, duodenal biopsy revealed features typical of the disease, but gastrointestinal symptoms were absent in all these cases. In all patients the vitamin E and B₁₂ levels were within the normal range. MRI of the central nervous system showed mainly cerebellar atrophy. In this study, no distinctive features of ataxia associated with CD which could differentiate it from other types of ataxia were found. Only late-onset of cerebellar symptoms were established [21].

In treating ataxia, a gluten-free diet should be started early in the course of the disease to stop the degeneration process of Purkinje cells. The timing of the elimination of gluten is crucial because in later stages of the disease the loss of Purkinje cells is irreversible [18, 20].

Epilepsy

The connection between epilepsy and CD is still unclear. Pratesi, Gandolfi, Martins et al. studied the frequency of occurrence of CD among epileptic patients. There were 255 patients in the study group and the control group was composed of 4405 individuals. The prevalence of CD (diagnosis confirmed on the basis of positive serological tests) was 2.3 times higher in the epileptic patients than in the control group (7.84/1000 vs. 3.41/1000). In two patients with epilepsy and CD, features of enteropathy in duodenal biopsy material were found. Both these patients had a history of difficult to control seizures. A 33-year-old woman had a long-lasting history of complex partial seizures, starting when she was 15 years old, which had never been completely under control although she was taking several different antiepileptic drugs. The patient was on a high dose of carbamazepine (65 mg/kg/day), but its blood levels were always in the low therapeutic range. Together with underweight, this suggested malabsorption syndrome. The second patient was a 3.5-year-old boy who first had generalized tonic-clonic seizures which progressed days later to frequent, short-lasting, complex partial seizures and brief and frequent atonic attacks. The tonic-clonic seizures continued to occur, mainly during sleep. An EEG examination suggested Lennox-Gastaut syndrome [22]. Cronin, Jackson, and Feighery compared the frequency of CD occurrence in a group of 177 epileptic patients and a control group composed of 488 pregnant women. Among the patients with epilepsy the frequency was 1/44 (4 individuals) and in the controls 1/244 (2 cases). In all 4 patients with CD, enteropathic features were found in duodenal biopsy specimens, but gastrointestinal symptoms (loose stools, abdominal bloating) were present in one patient. In one case, occult iron deficiency anemia was found. The authors, recalling earlier reports of the coexistence of CD, epilepsy, and cerebral calcification, typically bilateral in the cortical and subcortical regions in the parieto-occipital lobes, performed CT scans of 16 patients of Cork University Hospital who were diagnosed with CD and epilepsy. No patient had cerebral calcification [23].

Luostarinen, Dastidar, Collin et al. diagnosed CD in 2.5% (5/199) of adult patients with epilepsy of unknown origin, while the frequency of CD in the general population in this area was 0.27%. In 80% of patients (4/5) diagnosed with CD and epilepsy, CT head scans showed supratentorial brain atrophy, compared with 26% (33/125) of the patients without CD. This could indicate CD as one of the etiologic factors of the described, but still hypothetic, syndrome consisting of late-onset epilepsy and diffuse brain atrophy of unknown origin. Analysis of 130 CT scans revealed intracerebral calcifications in 11 (8.5%) patients with idiopathic epilepsy, but in none of them was CD diagnosed. The authors’ results support those of Cronin et al. suggesting that the coexistence of CD, epilepsy, and intracranial calcifications is sporadic. They also suggest that this clinical syndrome may be more frequent in patients of Mediterranean origin because most of the cases were described in Italian [24].

The pathogenesis of the association between CD and epilepsy remains unclear. One of the hypotheses points to the potential neurotoxicity of gluten, whereas the other suggests that pyridoxine or folate deficiency might lower the seizure threshold [26]. Praetsi et al., based on their own studies and those of other authors, listed some features characteristic of the coexistence CD and epilepsy. In many patients diagnosed with epilepsy, CD is asymptomatic or atypical. Early diagnosis and treatment of CD may prevent developing epilepsy and intracerebral calcifications, which are probably typical of later stages of the disease. Untreated CD leads to progression of epilepsy, it is at least difficult to obtain complete control of mainly complex partial seizures, and in some cases these difficulties may be caused by malabsorption due to enteropathy [22].
There are some reports which question the existence of an association between epilepsy and CD. In one of these, Ranua, Luoma, Auvinen et al. showed that the frequencies of EMA, TGA, and antigliadin antibody presence in a group of 968 epileptic patients were not different from those in 584 controls [25]. Dayangku, Pentgiran Tengah, Holmes et al., studying a group of 801 celiac patients, diagnosed epilepsy in 9 individuals (1.1% of cases), which was comparable to the frequency of epilepsy occurrence in the global population (0.5–1.0%) [26].

**Migraine**

Migraine is the most frequent subtype of primary headache. It affects about 15–18% of women and 6% of men [27]. There are some reports suggesting more a frequent occurrence of CD in the migraine patient population. In one of these, Gabrielli, Cremonini et al. diagnosed CD in 4.4% of patients suffering from migraine and in only 0.4% of controls. None of the patients complained of gastrointestinal symptoms. In the patients with CD and migraine, a gluten-free diet was applied for six months. In one of these patients the headaches completely resolved and in three others migraine improved in terms of frequency, duration, and intensity. In all the patients a SPECT study was performed to detect and localize alterations in cerebral blood flow. All the patients had evident abnormalities in regional cerebral blood flow before treatment with a gluten-free diet, and six months after starting the diet, SPECT showed a significant improvement in brain perfusion [27].

In a study mentioned by Bushar, the authors reported 10 migraine patients with positive serological tests for antigliadin antibodies, HLA DQ2 haplotype, and white-matter lesions on MRI. Nine patients responded to a gluten-free diet, with complete resolution of headache in 7 patients [19]. Recent studies have shown that serum antibodies of celiac patients strongly react with blood vessel structures in the brain. As an effect of autoimmune reaction there is a chronic release of various cytokines and other molecules with vasoactive properties, which may be a part of migraine’s pathogenesis [27].

**Schizophrenia**

Both CD and schizophrenia involve a genetic component. Individuals with a history of CD in childhood have an increased risk of developing schizophrenia later in life. Schizophrenic patients benefit from a gluten-free diet with improvement of psychotic symptoms. In their study, Wei and Hemmings present a hypothesis to explain the association between these diseases. In this hypothesis, a damaged permeability barrier in the gut plays the crucial role. Of crucial importance here would be defects in genes encoding structural proteins forming the tight junctions which create a regulated paracellular barrier to the diffusion of water and solutes through the paracellular pathway in the gut and the blood-brain barrier. The authors suggest that the more frequent association of schizophrenia and CD could be connected with an identical factor of origin initiating different pathogenic mechanisms. Gluten and potentially pathogenic components which can cause psychosis easily enter the body through a damaged permeability barrier in the gastrointestinal tract [28].

Based on the results of recent studies, it is not possible to form a definite opinion about a connection between schizophrenia and CD. Eaton, Mortensen, Agerbo et al. analyzed the medical files of 7997 patients suffering from schizophrenia. Four patients and eight patients’ parents were being treated for CD. Based on this they calculated the frequency of CD occurrence in the studied population as 1.5/1000, while in the control group it was 0.5/1000. This would mean a three-times higher risk of developing schizophrenia in celiac patients than in the general population [29]. The results of this study are controversial because the authors included the patients’ celiac parents in the study group; without this the percentage of CD patients in the group of patients with schizophrenia would be the same as in the control group.

There are some studies questioning an association between these two disorders. Peleg, Ben-Zion et al. compared the frequencies of positive serological test for EMA antibodies in a group of 50 patients diagnosed with schizophrenia and in a group of 50 mentally normal volunteers. All tests for antienzyme antibodies in both groups were negative; according to the authors it is unlikely that there is an association between gluten sensitivity and schizophrenia [30]. Ludvigson, Osby et al. determined the risk of non-affective psychosis in a population of patients diagnosed with CD. In the study were 14,003 celiac patients and a control group composed of 68,125 individuals. In the group of patients with CD there was a statistically significant increased risk of any non-affective psychosis (65 individuals, HR = 1.55), but this risk was largely due to the association with non-schizophrenic non-affective psychosis (56 individuals, HR = 1.61). There was no statistically significant association with subsequent schizophrenia (14 individuals, HR = 1.43) [31].
Depressive Disorders and Panic Disorders

Adult patients with CD more often show depressive symptoms. Previous studies suggested that impaired availability of tryptophan resulting from malabsorption and leading to decreased central serotonin synthesis might be involved in the development of psychiatric complications in CD. According to another hypothesis there is an immune activation with a T cell-mediated immune response to gluten which leads to cytokine and interferon-\( \gamma \) release. Increased interferon-\( \gamma \) production may suppress serotonin function both directly and indirectly, for example by enhancing tryptophan as well as serotonin turnover by means of increased activity of the kynurenine-niacin pathway. Gluten enteropathy which is not diagnosed in childhood would predispose for developing depression in adolescence, and a gluten-free diet could prevent the appearance of or improve depressive disorders [32, 33]. Hallert et al. examined cerebrospinal fluid in 10 adult patients who had been recently diagnosed with CD. In all the examined patients the concentrations of metabolites of serotonin (5-HIAA), dopamine (HVA), and noradrenaline (MOPEG) were determined. The patients were examined with MMPI scale 2 to estimate depressive symptoms. The study showed significant reduction in the levels of all the three major monoamine metabolites, indicating reduced central metabolism in all three monoamine pathways. The lower concentration of MOPEG inversely correlated with depressive symptoms [34]. Pynnönen, Isometsa, Aronen et al. studied the prevalence of mental disorders in a group of 29 celiac patients and in a control group also composed of 29 individuals. All celiac patients had enteropathy in duodenal biopsy. The frequency of a major depressive disorder in the group of adults diagnosed with CD was 31% and in the control group 7%; 21% of the celiac patients were diagnosed with double depression (dysthymic disorder superimposed on a major depressive disorder episode) versus 0% in the controls. Panic disorders were diagnosed in both groups with almost the same frequency: 21% in celiac patients and 24% in the control group. In most cases the diagnosis of CD was followed by depressive symptoms, which were present in patients with a positive parental history of depression [32]. Carta, Hardoy, Boi et al. compared a group of 36 celiac adults with a control group of 144 individuals without CD. The frequency of major depressive disorder among the celiac patients was ever higher than in the Pynnönen study: about 61.1 vs. 27.1% in the control group. The authors also studied the connection between autoimmune disorders of the thyroid gland with CD and mental disorders. Tests for the presence of the antithyroid autoantibodies were positive in 30.5% of the celiac patients and in 9.7% of the controls. Depression was diagnosed in 81.1% of the celiac patients with positive anti-TPO and in only 9.5% of the anti-TPO-negative patients [33]. These data suggest a higher risk of developing affective disorders in case of a coexistence of CD and subclinical autoimmune hypothyroidism. The authors presented two hypotheses to explain this connection. First, even a slight reduction in thyroid hormone secretion, such as that found in subclinical hypothyroidism, may affect cognition and mood. In contrast to other tissues that mainly rely on peripherally generated triiodothyronine, the brain preferentially utilizes circulating thyroxine directly secreted by the thyroid gland, so it is more responsive to hypothyreosis. According to the second hypothesis, the mechanism may be related to the autoimmune pathogenesis of thyroid disease and cytokines produced in immune reactions, which may exert an effect on the hypothalamic-pituitary-adrenal axis controlling neuroendocrine secretion and mood. Panic disorders were diagnosed in 22.2% of the celiac patients, while in about 3.5% of individuals of the control group. This kind of disorder was more frequent in celiac anti-TPO-positive patients, with 36.4% of cases compared of 4% of cases in the group with anti-TPO-negative tests. CD with coexisting subclinical autoimmune hypothyroidism increases the risk of panic disorders. A gluten-free diet does not seem to improve mental symptoms [33].

Addolorato, Capristo et al. studied the prevalence of panic disorders and depression among celiac patients and the influence of a gluten-free diet on the treatment of these disorders. The study group consisted of 35 celiac patients and the control group 59 individuals. Panic disorders were divided in two groups: those with dominating reactive anxiety connected with gastrointestinal symptoms (reactive panic disorder) and those with dominating anxiety as a personality feature (constitutional panic disorder). Among the celiac patients, reactive anxiety appeared more often than in the control group (71.4 vs. 23.7%). Depression was also diagnosed more often in the celiac patients than in the controls (appropriately 57.1% of cases vs. 9.6% of controls). The frequency of constitutional anxiety was more similar in both groups (25.7% of celiac patients vs. 15.2% of the control group). After six months of a gluten-free diet for the celiac patients, another psychiatric examination was performed. A decreased frequen-
cy of reactive panic disorder was reported; it was diagnosed this time in 25.7% of the patients, but no significant change was observed in the frequency of depressive disorders (45.7%) and constitutional panic disorder (17.1%). The authors suggested that the decreased quality of life of the patients and depressive disorders, which are present even on a gluten-free diet, are caused by the necessity to adhere to a very strict diet. They also mentioned that celiac patients, especially those without improvement with the gluten-free diet, need psychological support to control depressive disorders [35]. The study by Addolorato, De Lorenzi, Abenavoli et al. supports this statement. The authors examined a group of 66 celiac patients with anxiety and depressive disorders. The patients were randomized into two groups: in group A, psychological support was started at the beginning of the gluten-free diet period and in group B there was no psychological support. Both groups were followed every two weeks for six months. In the follow-up period, a significantly lower percentage of depressed patients was found in group A than in group B (15.1 versus 78.8%).

Psychological support did not reduce the percentage of depressed patients among patients without psychological support, a significantly lower compliance to the gluten-free diet was found (39% in group A vs. 9.1% in group B) [36]. The study by Roos, Karner, and Hallert showed a connection between psychological well-being and long-lasting gluten-free diet. Fifty-one celiac adults showing evidence of remission after 8–12 years of diet were examined by the Psychological General Wellbeing index. Long-treated patients showed no difference in psychological wellbeing from population controls, which suggests that signs of depressed mood are not a feature of well-treated CD patients [37].

Pynnönen, Isometsa, Verkasalo et al. studied the influence of a gluten-free diet on depressive symptoms and tryptophan concentration in the serum of celiac patients; before starting the gluten-free diet period, all the patients had significantly lower tryptophan concentrations. After three months on the gluten-free diet a significant decrease in psychiatric symptoms was found, coinciding with decreased CD activity and increased tryptophan concentrations. The results of this study support previous findings suggesting that serotonergic dysfunction due to impaired availability of tryptophan may play a role in the vulnerability to depressive and behavioral disorders [38]. To underline the role of mental disorders among patients with undiagnosed CD, a study by Hallert and Derefeldt is worth mentioning. It revealed that mental disorders (mainly depression) were, during the studied period of time, the most frequent cause of granting disability pension in patients with undiagnosed CD [39].

CD may often appears in an atypical form; then, extraintestinal symptoms dominate the clinical picture, frequently as neurological and mental disorders. Screening examinations for CD have to be performed in patients with nervous system disorders such as peripheral neuropathy, cerebellar ataxia, migraine, epilepsy, and mental disorders, especially depression and panic disorders. The mechanisms involved in this association and the influence of a gluten-free diet on neurological and mental disorders are still unclear and need further study [40, 41].

References


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