



## The progression of coeliac disease: its neurological and psychiatric implications

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### Abstract

The aim of the paper is to show the various neurological and psychiatric symptoms in coeliac disease (CD). CD is a T cell-mediated, tissue-specific autoimmune disease which affects genetically susceptible individuals after dietary exposure to proline- and glutamine-rich proteins contained in certain cereal grains. Genetics, environmental factors and different immune systems, together with the presence of auto-antigens, are taken into account when identifying the pathogenesis of CD. CD pathogenesis is related to immune dysregulation, which involves the gastrointestinal system, and the extra-intestinal systems such as the nervous system, whose neurological symptoms are evidenced in CD patients. A gluten-free diet (GFD) could avoid cerebellar ataxia, epilepsy, neuropathies, migraine and mild cognitive impairment. Furthermore, untreated CD patients have more symptoms and psychiatric co-morbidities than those treated with a GFD. Common psychiatric symptoms in untreated CD adult patients include depression, apathy, anxiety, and irritability and schizophrenia is also common in untreated CD. Several studies show improvement in psychiatric symptoms after the start of a GFD. The present review discusses the state of the art regarding neurological and psychiatric complications in CD and highlights the evidence supporting a role for GFD in reducing neurological and psychiatric complications.

**Key words:** Coeliac disease: Gluten-free diet: Neurological complications: Cognitive impairment: Psychiatric disorders

### Introduction

A new definition of coeliac disease (CD) has recently been presented by The European Society for Pediatric Gastroenterology, Hepatology and Nutrition, describing it as '... an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by a variable combination of gluten-dependent manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy<sup>(1)</sup>. Transglutaminase (tTG), a multifunctional enzyme tissue, has been widely reported to be a major auto-antigen in CD. The identification of IgA auto-antibodies directed towards this self-protein is crucial in the diagnosis of CD. The CD pathogenesis has also been reported to strongly involve tTG through the deamidation of gluten peptides that, once modified, are more easily presented to the immune system via human leucocyte antigen (HLA)-DQ2 or via DQ8 molecules. Gluten peptides reach the lamina propria and are presented to the T cells. Subsequently, several biological processes are triggered, leading to an increased T cell influx, crypt hyperplasia, and villous shortening in the proximal small intestine. As far as the prevalence of CD is concerned, many investigations are in accordance in evidencing that this disease is becoming more frequent in several geographical areas.

Nowadays, CD epidemiology is characterised not only by an increase in the cases reported in Northern Europe and the USA (historical areas of the spreading of CD), but also by its manifestation in different and new regions, such as Asian countries. This could be explained by the significant changes in the eating habits of these populations, who have increased the use of gluten especially during their childhood<sup>(2)</sup>. The way in which the disease changes and its clinical manifestations have been reported over time. Diarrhoea and malabsorption are not as frequent as they used to be in the initial stage of CD, among both adults and children. On the other hand, there has been an increase in non-specific signs and atypical manifestations<sup>(3)</sup>. Furthermore, CD signs and symptoms are no longer limited only to the gastrointestinal tract, as reported in the past, but more than half of adult patients show extra-intestinal manifestations that are also expected to be improved by a gluten-free diet (GFD)<sup>(4)</sup>. To date, the only treatment for CD with complete remission of symptoms is a lifetime diet with the total elimination of gluten. Even the ingestion of small amounts of gluten can cause major disruptions; therefore following a gluten-free regimen can lead to the relief of the symptoms, the normalisation of histological and laboratory findings and a decrease in the risk of CD's associative complications. For this reason, CD should be considered as a complex disease as well as a multifactorial pathogenesis to be

**Abbreviations:** CD, coeliac disease; CNS, central nervous system; EEG, electroencephalogram; GFD, gluten-free diet; HLA, human leucocyte antigen; IEC, intestinal epithelial cell; IEL, intra-epithelial lymphocyte; IFN, interferon; NK, natural killer; QOL, quality of life; SBD, sleep breathing disorders; SCZ, schizophrenia; tTG, transglutaminase.

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investigated from a genetic, biological and environmental point of view also considering the nervous system and its implications. This review aims to describe the detailed research on CD, highlighting its findings in different domains (genetics, environmental triggers and immune pathogenesis), focusing on more recent areas of investigation connected with neurological complications, cognitive impairment, psychiatric disorders and the impact of quality of life (QOL) in coeliac patients. Research undertaken demonstrates that good adherence to a GFD may also be extremely beneficial to both neurological and psychiatric symptoms.

Notably, the role of the GFD in subclinical neurological abnormalities has not been assessed and the impact on histological course needs further investigation. It is well established that the GFD represents the most important aspect of the management of CD patients and it is the only treatment that allows the prevention of several associated malignant and non-malignant complications, including neurological and psychiatric diseases.

## Pathogenesis

### Genetics

Recent studies in CD show that the disease is the interaction between genetic, environmental and immunological factors. The strongest and best-characterised genetic susceptibility factors in CD are HLA, especially the so-called DQ genes. The evidence of a genetic component in CD is best illustrated by the strong dependence on the presence of the HLA-DQ2 and HLA-DQ8 haplotypes<sup>(5–7)</sup>, most probably due to their physicochemical properties<sup>(8,9)</sup> and binding of specific peptides dominated by tissue tTG2. A Europe-wide collaborative study reported that only 0.4 % of CD patients were neither DQ2 (including the half heterodimer) nor DQ8 carriers<sup>(10)</sup>. Two additional studies carried out in the USA and Italy supported these findings by reporting a prevalence of DQ2/8 negativity in CD ranging from 0.16 to 0.9%<sup>(11,12)</sup>. When clinical suspicions are strong and supported by serological and histological findings in small samples of patients, CD can be diagnosed in the absence of HLA-DQ2 or -DQ8. Recently, genome-wide association studies have been able to identify several common non-HLA genetic factors associated with CD that account for a small amount of the overall risk. These genes have been reported to also be involved in adaptive and innate immune responses.

It should be noted that each of these non-HLA genes, taken separately, is not expected to play a major role in CD<sup>(6,7)</sup>. A study has also reported an association between HLA-G gene polymorphisms and susceptibility to CD development, suggesting the involvement of the HLA-G molecule in the pathogenesis of the disease<sup>(13)</sup>.

### Environment

It is clear that environmental factors play an important role in CD pathogenesis. The major environmental trigger is the intake of gluten. The problem lies in the high content of glutamine and proline concentrated in these proteins that make them

impossible to be completely digested by humans<sup>(6)</sup>. Individuals genetically predisposed to CD undergo a process by which the partially residual digested peptides set off an innate and adaptive immune response, thus considering a GFD to be the only effective treatment for CD to date. There may be other trigger factors in the development of the disease that could account for the considerable variability in the age of onset and in the clinical manifestations of the disease. Current studies have focused on these other factors such as the gut microbiome and its role in contributing to disease onset<sup>(14)</sup>, or the lack of breast-feeding<sup>(15)</sup>. As far as the latter is concerned, several researchers have identified a relationship between breast-feeding and the development of CD<sup>(15,16)</sup>. Both the duration of breast-feeding and the delay until gluten is introduced have been associated with a decrease in the risk of developing CD, though its cause still remains unknown. Nevertheless, other studies do not support this hypothesis. Indeed, A study of Italian children with a familial risk of CD<sup>(17)</sup> showed that neither the delayed introduction of gluten nor breast-feeding modified the risk of CD development among infants at risk, although the introduction of gluten at a later time is associated with a delayed initiation of the disease. Another study showed no effect of the timing of gluten being introduced on the incidence of CD in children at risk<sup>(18)</sup>.

Furthermore, studies report differences in the microbiota of breast-fed and formula-fed infants<sup>(19)</sup>. It has been reported that the microbiota, as well as nutritional and immune system-supporting factors in breast milk, could contribute to a decrease in gastrointestinal illnesses. Interestingly, infections by a variety of pathogens (for example, adenovirus 12 and hepatitis C virus (HCV)), have been associated with CD<sup>(20)</sup>. Moreover, the risk rate for CD diagnosis and the age of onset seemed to increase in children with CD-associated HLA genes after one or more rotavirus infections<sup>(21,22)</sup>. In addition, epidemiological studies report that individuals with CD were likely to be born during the summer period, meaning that the introduction of solid food, which occurs around 6 months of age, is concurrent with the seasonal peak of gastrointestinal illnesses in the winter period<sup>(23,24)</sup>. There is no clear evidence of a direct relationship between infections and the onset of CD, but it has been suggested that rotaviruses and other intestinal pathogens can create a pro-inflammatory environment and increase intestinal permeability<sup>(25)</sup>, thus enhancing the immune response to dietary antigens. In response to viral infections, there is a production of interferon (IFN)- $\alpha$  that enhances the activation of the Th1 response to anti-CD3 in the small intestine, leading to an increase in crypt hyperplasia<sup>(26)</sup>. Studies report numerous cases of patients with HCV who, after being treated with IFN- $\alpha$  therapy, developed CD, thus supporting a possible role played by type I IFN in the induction of the disease<sup>(27,28)</sup>.

### Immunopathogenesis

Immune dysregulation has been the core feature examined over the last few decades. Before addressing the issue of immunopathogenesis, an explanation of the amino acid composition of gluten is necessary. Gluten is comprised of two different protein types, gliadins and glutenins, which trigger the disease<sup>(29,30)</sup>.

Peptides in barley and rye, hordeins and secalins are also capable of activating CD while oats, with its more distantly related peptides called avenins, rarely trigger CD<sup>(31)</sup>. Due to their high content of prolines and glutamines, gliadins, glutenins, hordein and secalins are resistant to the degradation of gastric acid, pancreatic and brush-border enzymes, due to the lack in prolyl endopeptidase activity<sup>(32)</sup>. Undegraded peptide fragments can be transported across the epithelium primarily by transcellular pathways, such as tight junctions, which contribute to the balance between tolerance and immune responses to non-self antigens<sup>(33)</sup>. Zonulin, an endogenous modulator of epithelial tight junctions, triggers the paracellular trafficking of macromolecules. An increase in the secretion of zonulin is produced by gliadin, altering intestinal permeability and facilitating the transport of gluten, and triggering an inflammatory process. At the initial stage of the disease, exposure to gliadin induces directly the opening of tight junctions secondary to zonulin up-regulation and produces an increase in the paracellular passage of antigens in the gut submucosa<sup>(34)</sup>. Peptide fragments from wheat, rye and barley that are not digested are transported to the lamina propria, where they undergo the process of deamidation by tTG2 resulting in the conversion of glutamine into glutamate which in turn introduces negative charges with a stronger binding affinity for HLA-DQ2 and -DQ8 on antigen-presenting cells<sup>(35,36)</sup>. It is worth noting that gluten peptides that can be modified through deamidation are numerous, thus broadening and amplifying the gluten-specific T-cell response in the lamina propria<sup>(37)</sup>. It has been demonstrated that CD4<sup>+</sup> T cells produce most of the CD features<sup>(38)</sup>, recognising the gluten peptides bound to HLA-DQ2-5 or HLA-DQ8<sup>(39)</sup>, and amplifying the T-cell response through tTG2. Bodd *et al.*<sup>(40)</sup> have reported that T cells reacting against transglutaminase deamidated gliadin are IFN- $\gamma$ -secreting cells. IFN- $\gamma$  induces the production of matrix metallo-proteases<sup>(41,42)</sup> leading to the alteration of the epithelial barrier function<sup>(3)</sup>. Moreover, both IFN- $\gamma$  and TNF- $\alpha$  are reported to increase intestinal permeability by the disruption of tight junctions<sup>(43)</sup>. On the other hand, antigen-presenting cells generate IL-12 and IL-15, which are responsible for the promotion of the Th1 differentiation, survival and proliferation of gluten-specific CD4<sup>+</sup> T cells<sup>(44)</sup>. CD4<sup>+</sup> T cells respond with the secretion of proinflammatory cytokines controlling local inflammation, such as IFN- $\gamma$ , IL-2 and IL-21<sup>(40,45)</sup>. These cytokines act not only at a local level, but they also cross the basement membrane and bind receptors on the intestinal epithelial cells (IEC) and intra-epithelial lymphocytes (IEL)<sup>(7)</sup>. In the epithelium, IFN- $\gamma$  promotes IEC death and possibly IL-15 production by IEC<sup>(46)</sup>. *In vitro* studies have shown that IL-15 can activate T-cell receptor  $\alpha\beta$  (TCR $\alpha\beta$ ) IEL, leading to an increase in surface levels and activity of NKG2D (natural killer (NK) group 2D), the receptor for MHC class I polypeptide-related sequence A (MICA)<sup>(47)</sup> which can be found on the membrane of the CD8<sup>+</sup>  $\alpha\beta$  T cells,  $\gamma\delta$  T cells and most NK cells<sup>(48)</sup>, resulting in death. It is noted that CD patients who suffer from CD have an increase in both the expression and function of NKG2D in TCR $\alpha\beta$  IEL<sup>(49)</sup>. It is suggested that, following NKG2D–MICA interaction, the TCR $\alpha\beta$  IEL become activated, and kill the IEC, thus contributing to epithelial pathology because the IEL are reprogrammed to

become NK cells<sup>(48)</sup>. Furthermore, it has been shown that the expression of epithelial cell surface ligands, including MICA, is increased by IL-15, thus contributing to epithelial changes and other pathological processes associated with CD, which include the refractory CD type 2 and enteropathy associated T-cell lymphoma<sup>(50,51)</sup>. The interaction between IL-15 and the CD4<sup>+</sup> T cells is a necessary and sufficient condition to activate the CD8<sup>+</sup> T cells and damage the small intestine<sup>(38)</sup>. Usually acting as an autocrine growth factor, IL-21 has shown to have several functions. In the epithelium, the IEC are stimulated to produce CCL20, a T-cell chemoattractant, and enhance the cytotoxicity of the IEL. In the lamina propria, it is associated with the production of matrix metalloproteases by fibroblasts<sup>(52)</sup>, supporting the growth and differentiation of B cells. IL-21 also supports B cells in the production of IgA antibodies, specific for TG2 or deamidated gliadin<sup>(53)</sup>. Finally, IEC produce IL-7 and IL-15 which promote the activation and survival of IEL<sup>(54)</sup>. The activated IEL, in turn, have the ability to kill IEC. Furthermore, the activation and clonal expansion of B cells is driven by the activated CD4<sup>+</sup> T cells, through the production of Th-2 cytokines, so that B cells differentiate into plasma cells and produce antigliadin and anti-tTG antibodies<sup>(55)</sup>. These processes are thought to contribute to several features of CD pathology such as increased IEL numbers, villous atrophy, and the production of disease-specific antibodies, with the effect of producing inflammation, malabsorption and numerous secondary symptoms<sup>(56)</sup>.

### Neurological complications and cognitive impairment in coeliac disease

CD is primarily an intestinal disorder characterised histologically by intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy. This broader view of the disease seen as an inflammatory disease is supported by clinical observations of extra-intestinal manifestations such as dermatological, hepatic, osteological, endocrine and neurological signs<sup>(57)</sup>. The most severe neurological symptoms are dementia, amnesia, ataxia, acalculia, epilepsy, chronic neuropathies, confusion, personality changes<sup>(58)</sup>, cognitive deficits<sup>(59)</sup>, multifocal encephalopathy, neuromyelitis optica, muscular hypotonia, delayed motor development<sup>(60)</sup> and headaches<sup>(61,62)</sup>, some of which could improve with GFD treatment<sup>(61,63)</sup>.

Due to high levels of antigliadin antibodies, CD is seen as the common cause of neurological syndromes, particularly cerebellar ataxia, whose origin remains unknown. There is an increasingly wider spectrum of neurological syndromes identified both as complications of prediagnosed CD and as an initial manifestation of CD<sup>(64)</sup>. Studies show that the nervous system is compromised and acts as a complication in the pre-diagnosis of CD. Many studies have reported the involvement of the nervous system mainly as a complication of prediagnosed CD<sup>(61,65)</sup>. Several studies have investigated the prevalence of neuronal hyper-excitability and electroencephalogram (EEG) abnormalities in asymptomatic children and adolescents with newly diagnosed CD before the introduction of a GFD, and in particular any changes following the introduction of a diet.

A recent study evaluated the role of a GFD on neurological symptoms, EEG characteristics and sleep breathing disorders (SBD) in children with CD<sup>(61)</sup>. The authors enrolled nineteen children with a new biopsy CD diagnosis. At the diagnosis of CD, 37% of the patients complained of headaches and other neurological disorders that affected their daily activities and 32% of the patients were positive for SBD. The EEG tests revealed abnormal findings in 48% of children. After 6 months of a GFD, headaches and EEG abnormalities disappeared in most of the children in turn, resulting in them being negative for SBD. Asymptomatic children and adolescents manifested hyper-excitability and EEG abnormalities before a GFD. Adherence to a GFD has been shown to result in lighter headache symptoms reported by CD patients<sup>(62)</sup>. Results of functional imaging studies such as single photon emission computed tomography were in favour of migraines, and a GFD could lead to an improvement of migraine in these patients<sup>(66)</sup>. Functional imaging studies revealed migraines present through single photon computed tomography with the result that a GFD could lead to an improvement. However, an association between CD and migraine headaches was not established when compared with the general population<sup>(67)</sup>.

Other common neurological symptoms of CD are ataxia and epilepsy. Cerebellar ataxia is one of the first symptoms<sup>(68)</sup>, and one of the most frequently recognised neurological disturbances in CD<sup>(69)</sup>. Its predominant clinical manifestations include dysarthria, dysphonia, pyramidal signs, abnormal movements of eyes and progressive ataxia of gait. Ataxia related to CD is not often associated with typical gastrointestinal symptoms or malabsorption signs. Ataxic symptom relief has been reported with the adherence to a GFD<sup>(70)</sup>. Regarding epilepsy, several studies have demonstrated a relationship between epilepsy and CD, with prevalence rates ranging from 3.5 to 7.2%<sup>(64,69)</sup>. However, although epilepsy is considered in international studies as a condition associated with CD or an extra-intestinal manifestation of this disease, a recent study has not confirmed this association<sup>(60)</sup>.

Recent data are less consistent and vary below these figures<sup>(71)</sup>. Peripheral neuropathy is the second most frequent neurological complication in CD patients and has been reported in up to 50% of cases<sup>(61,72)</sup>. Neuropathy may precede a diagnosis of CD<sup>(73)</sup>. Research findings regarding the effect of a GFD on peripheral neuropathy have been mixed, with some reports indicating positive outcomes and others reporting no significant changes<sup>(63,74)</sup>.

A study which investigated neurological damage and gluten-free foods showed that neurological peripheral disorders, and autonomic dysfunctions with anti-neuronal antibodies in adults with CD did not disappear with a GFD<sup>(75)</sup>. On the contrary, important evidence comes from a case report of a 14-year-old patient with rare neurological symptoms<sup>(76)</sup>. The patient presented headaches and blurred vision for 1 year; she was diagnosed with papilloedema after an ophthalmic examination showing increased cerebrospinal fluid putting pressure on the backbone and was further diagnosed with pseudotumor cerebri. However, upper gastrointestinal endoscopy with duodenal biopsy confirmed the diagnosis of CD. The patient was put on a GFD, resolving the gastrointestinal symptoms and

also reaching almost complete resolution of the pseudotumor cerebri symptoms.

Neurological signs are rare in children but as many as 36% of adult patients present neurological changes<sup>(77)</sup>. Other neurological manifestations are tremor, myelopathy, brainstem encephalitis, progressive leukoencephalopathy, vasculitis, occipital calcification and myoclonic syndrome. A myoclonic syndrome, often accompanied by ataxia, may occur in CD. Myoclonus may be present as focal, multifocal or generalised convulsions. They also include neuromuscular manifestation such as peripheral polyneuropathy, mono-neuropathy multiplex, dermatomyositis, polymyositis and inclusion body myositis<sup>(67)</sup>. Additionally, one study showed that there is no significant difference between the laboratory data of the coeliac patients with and without neurological manifestations<sup>(78)</sup>. The neurological symptoms are headaches, epilepsy, migraines, mental retardation, breath-holding spells, ataxia, cerebral palsy, attention-deficit/hyperactivity disorder, Down's syndrome and Turner syndrome in order of frequency. Moreover, the 3a biopsy type was statistically more common among patients without neurological manifestations, while the 3b biopsy type was statistically and more common among patients with neurological manifestations. It is important to keep in mind that in the clinical course of CD, different neurological manifestations may be reported.

Although a range of neurological disorders are widely reported to be associated with coeliac patients, their pathogenesis remains unclear. Such disorders are believed to be secondary to vitamin deficiency due to malabsorption, and others to immune mechanisms. A further detailed study confirmed the role of hyperhomocysteinaemia for neurological features associated with CD<sup>(79)</sup>.

Neurological conditions have been researched in detail as opposed to cognitive functioning. CD adult patients reported milder forms of cognitive impairment known as 'brain fog', a symptom which disappears after GFD treatment but re-presents itself again after inadvertent gluten exposure<sup>(80)</sup>. Brain fog is characterised by the difficulty in concentrating, problems with attentiveness, short-term memory lapses, difficulties in word-finding, temporary loss in mental acuity and creativity as well as confusion and/or disorientation<sup>(81)</sup>.

A retrospective study on patients with a CD diagnosis after the age of 60 years presented evidence supporting the likelihood of such a link. Two patients out of seven presented a cognitive decline, initially attributed to Alzheimer's disease, but they showed an improvement in their symptoms after the initiation of a GFD. A third of the patients suffered from a peripheral neuropathy, and completely recovered following a gluten-free regimen<sup>(82)</sup>. The level of cognitive function was believed to have improved together with mucosal healing, an hypothesis proposed by Lichtwark *et al.*<sup>(80)</sup> in their longitudinal pilot study which investigated the relationships between cognitive function and mucosal healing in individuals diagnosed with CD starting a GFD. The study tested eleven patients (eight females, three males), mean age 30 (range 22–39) years, on a battery of cognitive tests at 0, 12 and 52 weeks. The items under examination were information, processing efficacy, memory, visual-spatial ability, motoric function and attention. Researchers also collected small bowel



biopsies via routine gastroscopy at 12 and 52 weeks so that cognitive performance could be compared with serum concentrations of tTG antibodies, with biopsy outcomes and with other biological markers. The results of the paper showed that tTG antibody concentrations decreased from a mean of 58.4 at baseline to 16.8 U/ml at the 52nd week, while four of the cognitive tests assessing verbal fluency, attention and motoric function reported significant improvement over the 12 weeks, besides confirming that improvement in cognitive performance was parallel to mucosal healing. The study reported an excellent adherence to the diet by all patients.

In addition, a study by Casella *et al.*<sup>(83)</sup> evaluated the functional and cognitive performance in CD patients diagnosed at the age of 65 years or older, compared with age- and sex-matched control patients using psychometric tests to obtain comprehensive information on functional performance, and general or more specific cognitive functions. The results evidenced how cognitive performance is worse in the elderly than in control patients, despite a longer time on a GFD<sup>(83)</sup>.

Several studies have investigated the relationship between dementia and CD<sup>(59)</sup>. Dementia develops as acalculia, confusion, amnesia and personality disorder<sup>(82)</sup>. However, the aetiology and specific treatment of this complication are not clearly known<sup>(67)</sup>. Collin *et al.*<sup>(84)</sup> reported five cases of patients with CD who developed dementia before the age of 60 years. Four patients suffered intellectual deterioration ranging from moderate to severe. In addition to intellectual deterioration, one patient showed deficit in both verbal and visual memory. One had slow psychomotor functions, and the other showed severe memory deficit, constructional deficit and apraxia. The fifth patient had deficits in digit span, visual memory, and visual-motor constructional difficulties. Brain computed tomography revealed diffused cerebral or cerebellar atrophy in all patients<sup>(84)</sup>. Other studies have reported a link between dementia in individuals diagnosed with CD after the age of 60 years. A retrospective study in Israel examined seven patients diagnosed with CD after the age of 60 years. Of the seven, two female patients were initially diagnosed with dementia of the Alzheimer type due to a progressive cognitive decline. Compliance to a GFD ameliorated the cognitive decline in both patients<sup>(82)</sup>. However, in another study, adherence to a GFD resulted in no change in neurological symptoms in patients with CD who presented mild memory impairment<sup>(85)</sup>.

### Psychiatric disorders and quality of life of coeliac disease patients

The association of CD with psychiatric disorders, including depression, has been identified for a long time. Several psychiatric symptoms have been reported as common complications in many patients suffering from CD, though the effects of diet on one's mood and psychiatric symptoms remain largely unknown<sup>(86)</sup>. Psychiatric symptoms usually described in CD patients include depressive symptoms, apathy, excessive anxiety, irritability<sup>(65)</sup>, eating disorders<sup>(87)</sup>, attention-deficit/hyperactivity disorder<sup>(88)</sup> and autism<sup>(89)</sup> as well as sleep disorders which are also common in CD. Sleep disorders are

related to depression, anxiety and fatigue, and inversely related to QOL<sup>(90)</sup>.

Carta *et al.*<sup>(91)</sup> suggests that the possible causative factors are malabsorption and nutritional deficiencies (especially of vitamin B<sub>6</sub> and tryptophan) and the association with other autoimmune diseases such as thyroid disease. A study on untreated CD patients reported decreased plasma levels of tryptophan and other monoamine precursors and decreased cerebrospinal fluid levels of serotonin, dopamine and noradrenaline metabolites (5-hydroxyindoleacetic acid, homovanillic acid and 3-methoxy-4-hydroxyphenylglycol, respectively)<sup>(92)</sup>. A cross-sectional, case-control study enrolling thirty-six CD patients used the Composite International Diagnostic Interview to assess lifetime psychopathology. The findings showed that the risks of major depression (41.7%), dysthymic disorder (8.3%), adjustment disorders (30.5%) and panic disorder (13.9%) are higher in CD<sup>(91)</sup>.

A meta-analysis on anxiety and depression in CD found that depression is more common and more severe in adults with CD compared with normal controls. However, depression in adults with CD did not differ from adults who had other physical illnesses and no differences in anxiety were found<sup>(93)</sup>. Additional studies have also found increased rates of depressive and anxiety symptoms in CD patients on a GFD<sup>(94,95)</sup>, though the prevalence of depressive symptoms in CD patients varies widely across studies ranging from 6 to 69% as shown by another large longitudinal population-based cohort study<sup>(96)</sup>, where CD patients were also reported to have an 80% increased risk of depression compared with controls. This variability in prevalence could be accounted for by differences in personal characteristics, cultural background and study design. The increased risk of depressive symptoms in CD patients could be explained by several mechanisms.

The first mechanism could be dietary non-compliance and sustained malabsorption, which could lead to sustained nutritional deficiencies (for example, vitamin B<sub>6</sub>, vitamin B<sub>12</sub> and folic acid) producing the risk of depression<sup>(97)</sup>. Second, a restrictive GFD could cause nutritional deficiencies. Even though these nutritional deficiencies contribute to the risks of depression, it is not established to date<sup>(98)</sup>. Depression could also be induced by reductions in brain monoamine availability and metabolism<sup>(92)</sup> and regional cerebral hypoperfusion<sup>(99)</sup> in patients suffering from CD. Delgado *et al.*<sup>(100)</sup> suggested excessive cytokine secretion due to chronic immune system activation as a fundamental pathology underlying depressive symptoms. Furthermore, there is an increased hypothalamic-pituitary-adrenal axis hyperactivity due to the cytokine activation associated with major depression<sup>(101)</sup>. Another reason can be found in the fact that, due to the strict dietary regimen, CD patients may avoid social situations involving food experiences. They may have higher levels of psychological distress because of daily difficulties, negative responses to the diet due to social surroundings and continuous worrying about dietary mistakes and negative results which could all lead to depression<sup>(102)</sup>. Finally, depression in CD patients may be a secondary condition resulting from the association between CD and other auto-immune diseases with a high risk of depression, such as thyroid disease and diabetes mellitus<sup>(103)</sup>.



Relationships between CD and psychiatric disorders such as anxiety and depression have been described especially when CD starts after 60 years of age<sup>(67)</sup>. It has been shown that children and adolescents with CD may have emotional and behavioural problems<sup>(104)</sup>. Most CD patients showed significantly higher scores of anxiety, harm avoidance, separation panic and somatic complaints, even after the introduction of dietary regimens. The introduction of a GFD results in a radical change in eating habits and lifestyle of CD children, and can be difficult to accept and stressful to follow. This induces a high level of anxiety, which may be evidenced in a different way according to gender susceptibility, resulting in depression in females and aggression and irritability in males. The acceptance of a GFD also depends on age. For example, adolescents aged between 12 and 17 years find it particularly difficult to adapt to their new dietary regimen. This is due to the fact that this age bracket already has to manage with social interactions with their peers and adults. Overall, reports highlight the fact of having a chronic condition during childhood and adolescence could prove difficult to manage. In this context, a strict food regimen can be considered a negative influence on their social life. On the whole, all these reports indicate that the impact of a chronic condition during childhood and adolescence may be difficult to manage<sup>(104)</sup>. On the other hand, another study demonstrated an association of increased depression and disruptive behavioural disorders in adolescents with untreated CD. This is evidence supporting the improvement in psychiatric symptoms after the initiation of a GFD<sup>(105)</sup>. A case-report also suggests that CD should be taken into consideration in children with psychiatric disorders, particularly if they are not responsive to psychotropic medication<sup>(106)</sup>. Given that unrecognised CD may predispose the sufferer to serious psychiatric disorders and behavioural problems, it should be considered as a differential diagnosis in all age groups. A recent study aimed to establish whether long-term adherence to a GFD can be related to depressive symptoms in CD patients, given that lifetime depressive symptoms may be present in at least one-third of CD patients on a GFD. The results of a recent study on long-term adherence to a GFD (5 years) evidenced a decrease in depressive symptoms producing relief of the symptoms as opposed to a short-term diet of less than 2 years<sup>(107)</sup>. It is worth noting that the elimination of gluten in the case of a patient suffering from chronic treatment-resistant symptoms of depression and anxiety showed significant improvement in the mental state and in routine activities. When anxiety and depressive symptoms persist even after an unsatisfactory reaction to pharmacological treatment, it indicates the need to identify the somatic reasons for the underlying condition<sup>(108)</sup>. Interestingly, a reduced QOL was highlighted in CD patients as compared with healthy control participants<sup>(109)</sup>.

Recent epidemiological data highlight the association between schizophrenia (SCZ) and several autoimmune diseases<sup>(110,111)</sup>, CD being one found to be in association with SCZ since the 1950s<sup>(112)</sup>. Studies on the effects of the elimination of gluten from the diet of SCZ patients have further strengthened the existence of an association between gluten and SCZ. In fact, SCZ patients whose symptoms improved after the introduction of

a cereal- and milk-free diet showed an interruption or reversal of clinical improvement towards wheat<sup>(113,114)</sup>. A few studies have suggested that SCZ and CD may be associated with similar or adjacent genes<sup>(115,116)</sup>. It has been reported that genetic susceptibility in SCZ lies in the HLA DQ, similarly to autoimmune disorders such as CD<sup>(117)</sup>. By contrast, a recent study showed no such HLA association in SCZ<sup>(118)</sup>.

The subsequent observations provided contrasting results. Epidemiological studies, for example the National Danish Register<sup>(119)</sup>, found that CD occurred before the onset of SCZ and that antibody-based diagnosis (above all anti-gliadin) was a risk factor for SCZ<sup>(118,120)</sup>. A study observed that anti-gliadin antibodies have a role in the aetiopathogenesis of SCZ<sup>(118)</sup>. An increasing number of studies suggest that the immune mechanisms are partially responsible for SCZ. Similarly to CD, an aberrant Th1 immune reaction has been connected with the development of SCZ. The study suggests a causal link between CD and SCZ: the risk for SCZ in CD patients may be dependent on the interplay between IFN- $\gamma$  and the transcription factor STAT1 (signal transducer and activator 1)<sup>(121)</sup>.

A recent study showed that bacterial compositions could explain the inefficient gluten digestion and how in certain situations can be a risk factor for SCZ because the gut microbiota contributes to digestion, inflammation, gut permeability and behaviour<sup>(122)</sup>. It is also significantly recognised that bidirectional communication exists between the brain and the gut that uses neural, hormonal and immunological routes. An increased incidence of gastrointestinal barrier dysfunction, food antigen sensitivity, inflammation and the metabolic syndrome is seen in SCZ<sup>(123)</sup>. As demonstrated, these symptoms can be influenced by the composition of the gut microbiota.

Another theoretical framework suggests that inappropriate oestrogen exposure occurring in the brain could also be occurring in the colon so that an association of CD or some other inflammation and SCZ may be observable not from a genetic link, but rather from a transgenerational effect of prenatal oestrogen exposure<sup>(120)</sup>.

There have been studies and case reports of a dramatic recovery from SCZ associated with the implementation of a GFD. A case report shows that there is a improvement in psychotic symptoms after a GFD in a young man with complex autoimmune illness<sup>(124)</sup>. The remission of psychotic symptoms in this patient was associated with the adherence to the diet. Regardless of the exact mechanism involved, the marked improvement in this patient's SCZ symptoms after the implementation of a GFD highlights the need for further research on the role of the diet in SCZ.

Another research group reported a case of brain perfusion abnormalities, assessed by single photon emission computed tomography examination, in a 33-year-old CD patient with SCZ, with the regression of both cerebral hypoperfusion and SCZ symptoms observed after 6 months of a GFD<sup>(125)</sup>. These findings may have potential implications for the treatment of these subjects given that a GFD can contribute to the improvement of their symptoms. In another case report, the symptoms of SCZ were improved in a coeliac patient after the introduction of a GFD<sup>(126)</sup>.

To date, CD adversely affects the QOL of individuals because of several factors such as its chronic nature, the impact on health, psychological distress, social and family connotations, and the need for lifelong treatment. While these factors are important for QOL, one area that has received less attention are the psychological symptoms and how to cope, despite the higher rates of psychological symptoms within CD patients compared with the general population.

There is proven evidence showing that when one suffers from CD it affects the general perception of their QOL and well-being and a GFD generates difficulties and limitations in the life of patients under treatment<sup>(127)</sup>. Even in the case of a considerable improvement in the symptoms, adhering to a GFD can be difficult for many individuals because of poor palatability and poor availability of GF products, thus resulting in a condition that can have serious repercussions on the QOL<sup>(128)</sup>. Casellas *et al.*<sup>(129)</sup> have recently reported that good adherence to a GFD resulted in an improved QOL using CD-QOL compared with patients with the intention of not complying. It could be affirmed that it is only with a complete adherence to a GFD that brings significant benefits for the health and QOL of coeliac patients in order that its drawbacks can be counterbalanced. In conclusion, the results of this study suggest that most coeliac patients who followed a GFD correctly showed a better QOL, measured by a specific instrument for coeliac patients and this was also associated with a good control of the symptoms<sup>(129)</sup>. It has been demonstrated that there is a direct link between the severity of gastrointestinal and psychological symptoms in coeliac patients and how their symptoms both have an impact on QOL<sup>(130)</sup>. This research is the first which investigates the medical impact of the disease and its psychological effects and how adherence to a GFD has effects on the QOL in CD. This study shows how poor adherence to a GFD reduces the QOL which in turn increases the psychological symptoms as well as severe gastrointestinal symptoms and difficulty in coping. These results represent major threats in achieving an adequate QOL. Early diagnosis and treatment of this disease could alleviate the symptoms which in turn could lead to a better QOL.

### Potential link between the intestine and the brain: the role of a gluten-free diet

Mental disorders that accompany digestive diseases constitute an interdisciplinary aspect to date not fully recognised and considered a diagnostic and therapeutic problem. The most recognised is CD in which patients suffer from a wide range of neuropsychiatric symptoms. It has not been fully explained how the pathogenic mechanism of CD affects the patient's mental health, but one hypothesis suggests that it is due to serotonin imbalance or opioid neurotransmission caused by the effect of gluten and gluten metabolites on the central nervous system (CNS)<sup>(131)</sup>.

Given that the gastrointestinal tract is connected to the CNS means that the communication involves neural pathways and immune and endocrine mechanisms. The intestinal barrier prevents toxins, pathogens and antigens in altering the various neuroactive compounds<sup>(132)</sup>.

The existence of a rich gut-to-brain communication raises the possibility that intestinal barrier alterations may take part in the pathophysiology of CNS disorders and determine neuropsychiatric symptoms<sup>(133)</sup>. To date there have been neurophysiological studies aiming to evaluate the gut–microbiota–brain axis<sup>(134,135)</sup> but these unfortunately have not yet involved coeliac patients. A study suggests that modulation of the gut microbiota may provide a novel therapeutic target for the treatment and/or prevention of mood and anxiety disorders<sup>(136)</sup>. Alterations in gut microbial composition is associated with marked changes in behaviours relevant to mood, anxiety and cognition, establishing the critical importance of the bi-directional pathway of communication between the microbiota and the brain in health and disease. Dysfunction of the gut–microbiota–brain axis has been implicated in stress-related disorders such as depression, anxiety and neurodevelopmental disorders such as autism and SCZ<sup>(137)</sup>.

Although communication between gut microbiota and the CNS are not fully elucidated, neural, hormonal, immune and metabolic pathways have been suggested. The concept of a gut–microbiota–brain axis is emerging, suggesting that microbiota-modulating strategies may be a tractable therapeutic approach for developing new treatments for CNS disorders and for neurological and psychiatric symptoms<sup>(138)</sup>. Several studies have reported the effect of a GFD on the composition of the gut microbiome in CD patients<sup>(139,140)</sup>. Patients with CD have a reduction in beneficial species and an increase in those potentially pathogenic as compared with healthy subjects<sup>(141)</sup>. Gut microbes can produce hormones and neurotransmitters and the bacterial receptors for these hormones influence microbial growth and pathogenicity. Gut bacteria directly stimulate afferent neurons of the enteric nervous system, sending signals to the brain via the vagus nerve<sup>(142)</sup>. Through these varied mechanisms, gut microbes induced reactivity of the hypothalamic–pituitary–adrenal axis which influence memory, mood and cognition and are clinically and therapeutically relevant to a range of disorders. In order to alter the gut microbiome therapeutically, changes in diet, probiotics and prebiotics are necessary<sup>(143)</sup>. Some reports show that in autism disorders, the use of diets such as gluten-free and casein-free diets may contribute to the improvement in behavioural symptoms following these dietary regimens<sup>(133)</sup>. In patients under a GFD, a global increase in cortical excitability was observed in one study, suggesting a glutamate-mediated functional reorganisation compensating for the progression of the disease<sup>(144)</sup>. It was hypothesised that glutamate receptor activation, probably triggered by CD related to immune system dysregulation, might result in a long-lasting motor cortex hyperexcitability with increased excitatory post-synaptic potentials, probably related to the phenomena of long-term plasticity. In this study, a certain degree of improvement of depressive symptoms was also observed, supporting the role of a GFD in the amelioration of psychiatric CD-related disorders. Another study reports that immune system dysregulation in patients with CD may play a central role in triggering changes in motor cortex excitability resulting in the manifestation of the symptoms<sup>(145)</sup>. This study suggested that cross-reaction between anti-gliadin antibodies and neuronal antigens, as well as altered levels of ions related to transglutaminase deposition 6-immunoglobulin, could affect the normal balance between excitatory and inhibitory

synaptic excitability. To emphasise the importance of these links, psychiatric or neurological patients may benefit from starting a GFD stressing the importance that there is a two-way communication between the brain and the gut that uses neural, hormonal and immunological pathways. In the future, scientific researches could prove that there is a link between the intestine and the brain, and that GFD could exert a role for the treatment of neuropsychiatric symptoms.

**Conclusions**

Based on current evidence, the present review proposes a comprehensive view of the pathogenesis of CD and explains the progression of its development and of its complications. From a genetic basis, the immunopathogenesis and above all the neurological or psychiatric implications of recent scientific studies where CD is becoming more complicated is discussed. The purpose of the present review was to investigate and illustrate the neurological and psychiatric complications in CD and the importance of a GFD given the symptoms. While some of these symptoms can improve with a GFD, our advice is to try to diagnose CD as early as possible, given that delays in the diagnosis may cause severe implications in the nervous system. The importance of early diagnosis is fundamental and the only treatment available is a GFD to be followed for a lifetime. It is therefore essential to follow nutritional therapy to avoid this kind of complication. Mental disorders accompanying digestive system diseases are interdisciplinary although poorly acknowledged. One of the most recognised examples is CD in which patients suffer from a wide range of psychopathological symptoms, which must be taken into consideration from both a diagnostic and therapeutic point of view. The above studies show that neuropsychiatric symptoms may represent an atypical manifestation of CD occurring before the gastroenterological diagnosis and the introduction of the diet causes a significant improvement in mental status. Bearing in mind these considerations, our review also claims that a GFD is effective in the treatment of depression, anxiety and neurological complications associated with CD<sup>(105,107)</sup>.

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