

A Review of Psychiatric Disorders Associated with Celiac Disease

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Abstract

Celiac Disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Although classic symptoms of CD primarily involve the gastrointestinal tract, extra-intestinal symptoms are common as well. In this review, we examine psychiatric disorders that occur in association with CD, examine pathophysiological mechanisms that may be responsible for these comorbid conditions, and suggest areas of research that could both improve our understanding and reveal potential new treatments for these psychiatric disorders.

Keywords: Gluten; Depression; Schizophrenia; Anxiety; Autism spectrum disorders; Eating disorders; ADHD

Introduction

Celiac Disease (CD) is an autoimmune enteropathy caused by an inappropriate immune response to gluten in genetically susceptible individuals [1]. Individuals with untreated CD are at increased risk for both gastrointestinal (GI) and extraintestinal problems. A subset of individuals with CD is at increased risk for psychiatric disorders [2]. The basis for this increased prevalence of psychiatric disorders in CD and the common pathophysiological mechanisms responsible for these comorbid disorders remain to be elucidated.

What is gluten?

The term gluten refers to a group of proteins found in wheat, barley, and rye consisting of gliadin and glutenin subcomponents [3]. When added to bread, gluten supports bread rising, provides elasticity, and helps bread keep its shape [4-6].

Gluten proteins are difficult to digest in the human GI tract due to their high proline content [7]. These undigested gluten proteins are toxic for individuals with CD [8].

What is Celiac Disease?

Celiac Disease is defined as a chronic, immunologically determined enteropathy precipitated by the ingestion of gluten-containing foods in genetically predisposed individuals [9].

Samuel Gee first described CD more than a century ago [10]. But, it wasn't until the 1940's that the Dutch pediatrician, Willem-Karel Dicke, identified wheat flour as the causative agent [11]. Many factors influence the onset and progression of CD including genetic predisposition and environmental influences.

Individuals with CD may exhibit a polymorphous clinical presentation. In children, characteristic features include malabsorption syndrome with growth failure, malnutrition, chronic diarrhea, steatorrhea, edema, abdominal distention, and muscle wasting [12]. Adults with CD manifest a wider range of symptoms than children [13].

Epidemiology of CD

The prevalence of CD varies widely throughout the world. In Europe and North America, about 1% of the population is affected [14]. Germany has one of the lowest prevalence rates (0.3%) [15] and the Saharawi population from Western Sahara has one of the highest (5.6%) [14].

The prevalence of CD has been found to be increasing with time [16]. The presence of serological markers for CD has quadrupled in the United States during the last 50 years [17] and doubled in Finland in the last 20 years [18]. This increase was observed in blood samples that were collected and frozen decades apart. Thus, the increase in CD cannot be attributed solely to improved detection or changes in diagnostic criteria. Also, serological markers for CD have been found to increase within the same group of individuals over time, indicating that an abnormal response to gluten can develop over the course of one's lifetime [19]. Possible explanations for the increasing prevalence of CD include higher gluten content in many current wheat varieties and increased consumption of wheat [20].

The majority of individuals with CD remain undiagnosed. This fact has been illustrated by the concept of a "celiac iceberg" in which the overall prevalence of CD equates to the total size of the iceberg, diagnosed cases represent the tip of the iceberg visible above the water line, and the submerged portion of the

iceberg represents individuals with undiagnosed CD [21]. There are an estimated 5-10 undiagnosed cases for every diagnosed case of CD [13].

Pathophysiology of CD

CD is a multifactorial disease with both genetic and environmental factors contributing to the development of this disorder.

Genetic factors: The high incidence of CD in 1st-degree relatives of celiac patients (10-15%) and high concordance rate in monozygotic twins (80%) suggest a strong genetic component. The main determinants of genetic susceptibility to CD are the major histocompatibility class II HLA molecules. More than 90% of individuals with CD carry one or two copies of the HLA-DQ2.5 gene. DQ2-negative CD patients are almost invariably HLA-DQ8 positive [22,23].

The DQ2 and DQ8 haplotypes are necessary, but not sufficient, for the development of CD. These haplotypes are expressed in 98% of people with CD, 90% of people who are unaffected but have a relative with CD, and 55% of the general population [24]. However, only about 1% of the population will develop CD. Thus far, at least 39 non-HLA genes that confer a predisposition to CD have been identified, most of which are involved in inflammatory and immune responses [25].

Environmental factors: The environmental risk factor with the highest correlation for developing CD is exposure to gluten. Other risk factors include region of birth [26,27] and season of birth [28,29]. Children born in the winter have a lower risk of developing CD than children born in the spring or summer [26,28,29].

Changes in gut microbiota and infection with certain viruses also increase the risk of developing CD [30-33]. Being born by elective caesarean section rather than vaginal delivery is another risk factor for CD [24].

The impact of breastfeeding and timing of gluten introduction on the subsequent development of CD remain controversial, with some studies indicating a positive association [34,35] and others reporting no association [24,36-38].

Pathogenesis of CD

The development of CD begins when dietary gliadin binds to CXCR3 receptors in the intestinal epithelium in genetically susceptible individuals [39]. This triggers the release of zonulin [40], a protein involved in the regulation of intercellular tight junctions [41]. Tight junctions represent the major barrier in the paracellular pathway [40,42,43]. Increased levels of zonulin cause loosening of tight junctions, resulting in disruption of the mucosal barrier and increased intestinal permeability [9].

Certain gluten peptides are highly resistant to proteolysis by gastric, pancreatic, and intestinal digestive proteases due to a large number of proline and glutamine residues [44]. Increased intestinal permeability resulting from increased zonulin allows these intact gluten peptides to cross the intestinal mucosa. After reaching the submucosa, proline and glutamine-rich gluten

peptides are deamidated by the enzyme tissue transglutaminase type 2 (tTG2), which has specificity toward proline-rich peptides. The left-handed helical conformation of proline-rich gliadin peptides renders them better substrates for tTG2 [45]. The resultant immunostimulatory epitopes have a high affinity for HLA-DQ2 and DQ8 molecules expressed on the surface of T lymphocytes. These deamidated gliadin epitopes bind to HLA-DQ2 and DQ8 molecules, triggering inflammatory and immune-mediated responses. The end result is damage to the mucosa of the duodenal tract, which is seen on biopsies as villous atrophy and crypt hyperplasia [12].

How is CD diagnosed?

Often, many years pass between the development of symptoms and the correct diagnosis of CD. The median duration of time from first symptoms to diagnosis ranges from 4.9 to 9.7 years [46,47]. This delay in diagnosis is associated with impairment in quality of life [47]. It is important for clinicians to have a good understanding of both the classic and extraintestinal manifestations of this disorder in order to consider CD in the differential diagnosis.

Definitive diagnosis of CD is based on a thorough assessment of the presenting symptoms, a high index of suspicion, serological testing, and histological analysis of duodenal biopsies. Recently, it has been suggested that high tTG2-antibody levels in a symptomatic patient have such high diagnostic accuracy that it may be possible to omit the duodenal biopsy [12].

Treatment of CD

Treatment of CD involves a gluten free diet (GFD) for life. A GFD involves a diet free from wheat, barley, rye and foods that have been cross-contaminated with gluten-containing foods. To be labeled "gluten-free," foods must contain <20 mg/kg of gluten. Maintenance on a GFD for as long as 2 years may be required for individuals with CD to make a full recovery [48].

A GFD reduces gut permeability [49] and zonulin levels [50]. This protects individuals with CD against the risk of developing other diseases associated with CD and normalizes their mortality. However, if untreated or neglected, CD is associated with numerous complications [13,51].

Novel therapies are being investigated as treatments for CD. Infliximab, a monoclonal antibody against tumor necrosis factor that is used in the treatment of autoimmune diseases, has shown promise in cases of refractory CD [52-54]. Other studies have investigated the synthetic zonulin-blocking peptide larazotide acetate as a potential treatment for CD [55-59]. In a single case study, a change in the gut microbiota resulted in full recovery from CD [60].

Extra-intestinal problems associated with CD

In addition to intestinal damage, CD is associated with a wide variety of extra-intestinal problems. These include: malignancies, dermatologic problems, neurologic disorders, dental enamel hypoplasia, rheumatologic conditions, chronic

hepatitis, cardiac disease, osteoporosis, endocrine disorders, autoimmune disorders, and psychiatric disorders [13,51,61-65].

This article examines the connection between CD and psychiatric disorders.

Methods

We conducted a PubMed literature search (1955-2016) looking for English language articles containing the search terms Celiac Disease (CD) and the following terms: depression (181 articles), bipolar disorder (11 articles), anxiety (80 articles), schizophrenia (96 articles), Autism Spectrum Disorder (ASD) (19 articles), Attention-Deficit/Hyperactivity Disorder (ADHD) (15 articles), and eating disorders (78 articles). All retrieved articles were screened and a subset of relevant abstracts was then selected for more detailed evaluation. The biographies of these articles were then searched for additional references. The final studies selected for inclusion in this review consisted of those articles that directly evaluated the association between Celiac Disease and the aforementioned psychiatric disorders.

Results

Comorbidity between psychiatric disorders and CD has been observed for more than 60 years [66,67]. Several psychiatric disorders are associated with CD, the most common being: depression, Bipolar Disorder, anxiety disorders, schizophrenia, Autism Spectrum Disorders (ASD), eating disorders and Attention-Deficit/Hyperactivity Disorder (ADHD).

Depression

An association between depression and CD was described more than half a century ago [68]. Subsequently, numerous studies have found depression to be more common in individuals with CD than in controls [69-76]. The prevalence of depressive symptoms in individuals with CD ranges from 6 to 69% [77]. A meta-analysis of 18 studies examining depression in adults with CD found depression is more common and/or more severe in adults with CD than in healthy controls (overall meta-analysis effect size: 0.97) [78]. An increased risk of suicide has also been reported in individuals with CD compared with controls [79].

Not all studies agree with the finding of an increased prevalence of depression in individuals with CD [80-84]. Some authors have suggested that depression occurring in CD patients is the result of having a chronic disease rather than being directly related to having CD [70] or is related to comorbid conditions, such as type 1 diabetes mellitus [80].

Bipolar disorder

Studies exploring a possible relationship between CD and Bipolar Disorder (BD) have produced mixed results. Negative findings include a population-based cohort study in Sweden that found individuals with CD were not at increased risk of developing BD [75] and a Danish study that found no familial relationship between autoimmune diseases and BD among 3.57

million individuals [85]. However, other studies describe an increased prevalence of BD among individuals with CD [86-89].

Elevated levels of antibodies associated with CD have been found in individuals with BD. Increased levels of IgG antibodies to gliadin were found in 102 individuals with BD, which was highly significant when compared with 173 controls without psychiatric disorders ($p < 0.0001$) [90].

In a subsequent study, individuals hospitalized for acute mania had significantly increased levels of IgG antibodies to gliadin, but no other markers of CD. At six-month follow-up, levels of IgG anti-gliadin antibodies were not significantly different from those of controls. However, among individuals with mania, those with elevated IgG anti-gliadin antibody levels at six-month follow-up were significantly more likely to be re-hospitalized [91].

In another study, levels of multiple autoantibodies were elevated in individuals with BD. The BD group had higher levels of one or more autoantibodies compared with controls (68.8% *versus* 39.6%; $p = 0.043$). Furthermore, individuals with BD were found to have twice as many autoantibodies per patient as controls. However, the difference was not statistically significant (1.5 *versus* 0.56; $p = ns$). Anti-gliadin IgG antibodies were significantly more prevalent in individuals with BD *versus* controls (50% *versus* 9.8%) [92].

These studies suggest IgG anti-gliadin antibodies might be a biomarker as well as a prognostic indicator in a subset of individuals with BD.

Anxiety disorders

Several studies have found an increased risk of anxiety disorders in individuals with CD. These include a report that found state anxiety to be present in a higher percentage of individuals with CD than controls, whereas no difference was found in trait anxiety. The authors interpreted this finding to indicate that anxiety is a reaction to the disabling symptoms of CD rather than a personality trait of the individuals who suffer with CD [69].

In a subsequent study, state anxiety was again found to be increased in individuals with CD compared to controls (71.4% *versus* 23.7%; $p < 0.0001$), but no difference was seen in trait anxiety (25.7% *versus* 15.2%; $p = ns$). After 1 year on a GFD, state anxiety symptoms improved significantly [93].

Individuals with CD were evaluated for Social Phobia using the Liebowitz Social Anxiety Scale (LSAS) in another study. The percentage of individuals with CD who were found to have Social Phobia was significantly higher than in controls (70% *versus* 16%; $p < 0.0001$). There was no difference in the number of subjects with Social Phobia who were newly diagnosed *versus* those who were on a GFD (73.3% *versus* 68%; $p = ns$) [94].

A study using the Hospital Anxiety and Depression Scale to assess the prevalence of anxiety disorders among individuals with CD found an increased prevalence of anxiety disorders in individuals with CD compared with controls (16.85 *versus* 5.7%; $p < 0.001$) [82].

Two studies evaluating Panic Disorder (PD) in individuals with CD found an increased risk of PD compared with controls (i.e. 13.9% versus 2.1%; $p < 0.001$ and 18.3% versus 5.4%; $p < 0.001$) [71,86].

Obsessive-compulsive behavior disorders have also been linked with CD. Individuals with CD who had been off gluten for a minimum of 1 year were evaluated using the Structured Clinical Interview for DSM (SCID) based on DSM-IV criteria to evaluate for axis I and II disorders. Twenty-eight out of 100 individuals with CD showed obsessive-compulsive behavior disorders whereas only 10 healthy controls were found to have anxiety disorders. Additionally, individuals with CD had significantly higher levels of both state and trait anxiety compared with controls ($p = 0.0001$ and $p < 0.0001$ respectively) [70].

Not all studies demonstrate a positive association between CD and anxiety, however. A meta-analysis involving eleven studies examined whether CD and anxiety are linked. Adults with CD were not found to differ reliably from healthy controls in terms of anxiety [78]. Other studies similarly found no statistical difference in anxiety between individuals with CD who were on a GFD and healthy controls [83,84].

Schizophrenia

The association between CD and schizophrenia may be the strongest of any psychiatric disorder [95]. In fact, psychosis can be the presenting symptom of CD [96].

More than 60 years ago, Bender [66] suggested children with schizophrenia were more likely to develop CD. Subsequently, four cases of CD among 37 adult males with schizophrenia admitted to the Institute of Pennsylvania Hospital over the course of one year were described [97] and additional case reports followed [98-100].

Studies examining the link between schizophrenia and gluten during World War II found hospital admissions for schizophrenia decreased in areas of lower grain consumption, whereas admissions increased in countries with higher wheat consumption [67,101]. A milk- and cereal-free diet was reported to improve schizophrenic symptoms, and inpatients on this diet were moved to a non-locked ward quicker than those with gluten added to their diet [102]. A follow-up investigation found schizophrenic patients on a GFD were discharged twice as quickly as those not on a GFD [103]. Over a decade later, fewer cases of schizophrenia were identified in countries where grain consumption was low. Furthermore, when grain consumption increased, the prevalence of schizophrenia increased also [104].

In a study of 7,997 people admitted to a Danish psychiatric hospital for the first time with a diagnosis of schizophrenia, CD was found to be a risk factor for schizophrenia. Individuals with CD had a 3.2 fold increased relative risk of developing schizophrenia ($p < 0.0001$) [105].

Reports of increased risk of schizophrenia in individuals with CD have generated controversy, however. A reexamination of the data linking schizophrenia with CD pointed out that if parents of individuals with schizophrenia were excluded from

the data, the prevalence of CD was no higher than in a control population [106]. In a study using data from the UK General Practice Research Database, no increased prevalence of schizophrenia was found in individuals with CD compared with the general population [107]. Also, in a study of 100 Iranian inpatients with schizophrenia, no increased rate of CD was found [108].

Explorations of the effects of a GFD on schizophrenic symptoms have demonstrated mixed results. While some studies show no effect [109-111], others demonstrate marked improvement in a subset of individuals with schizophrenia [112-115]. It has been suggested that the presence of antibodies to tTG or gliadin might be a biomarker that could help identify which schizophrenic individuals would respond to a GFD [114].

Several studies examining possible genetic and pathophysiological similarities between CD and schizophrenia have produced conflicting results. One study found abnormal intestinal permeability in individuals with schizophrenia [116], but this finding was not confirmed in a subsequent study [117]. A positive correlation was reported between plasma amino acid levels in individuals with schizophrenia and individuals with CD [118]. However, a reanalysis of the same data described this association as spurious [119].

Studies exploring a possible genetic linkage between CD and schizophrenia have also produced contradictory results [120,121]. A positive correlation between the amount of a leukocyte migration inhibition factor produced by peripheral blood lymphocytes following gluten challenge in individuals with schizophrenia and CD has been described [122].

In an effort to determine whether gluten might produce schizophrenic symptoms, intracerebral injections of gliadin polypeptides fractions were performed on rats. After high dose injections, reactions such as seizures, perseverative behaviors, and other unusual behaviors were noted. The authors suggested gluten might be related to the pathogenesis of schizophrenia [123]. A follow up report suggested schizophrenia was caused by neuroactive peptides produced during digestion of certain food proteins [124]. This hypothesis was supported by the finding that food-derived opioid peptides known as exorphins were present in gluten [125-127]. These peptides were subsequently studied as a possible common etiological factor in CD and schizophrenia [128]. A quarter of a century later, exorphins were reported to produce antioxidant and epigenetic changes [129]. Exorphins were also suggested to be responsible for the absence of classical GI symptoms in individuals with asymptomatic CD [130].

In the 1970's, studies were performed to investigate whether antibodies to gluten were more common in schizophrenic patients than in healthy controls. An increased frequency of anti-gliadin antibodies in hospitalized schizophrenic patients was found. However, these same antibodies were increased in hospitalized non-schizophrenic patients as well. The frequency in all psychiatric patients was more than six times higher than in healthy controls and was significantly higher than the frequency found in hospitalized non-psychiatric patients. The authors proposed sustained emotional distress increases the likelihood

of developing anti-gliadin antibodies by decreasing gut-barrier function, thus permitting the absorption of gliadin polypeptides [131].

In subsequent studies, individuals with schizophrenia were found to have elevated levels of antibodies to gliadin [132,133], tissue transglutaminase 6 (tTG6) [134], and *Saccharomyces cerevisiae* (a marker of intestinal inflammation) [135] compared with controls.

A meta-analysis examining biomarkers of gluten sensitivity in individuals with schizophrenia found five biomarkers were significantly elevated compared with controls. These were: anti-gliadin IgG, anti-gliadin IgA, anti-tTG2 IgA, anti-gliadin (unspecified isotype) and anti-wheat [136].

A different study found no correlation between selected antibody levels in individuals with CD and schizophrenia [137], although this study was criticized for its small sample size [138]. Other investigations found no difference in the incidence of reticulin antibodies between individuals with CD and schizophrenia [139,140], however, reticulin antibodies are no longer considered useful in the diagnosis of CD [141]. Schizophrenia patients and otherwise healthy CD patients were tested for antibodies to tTG2 and deamidated gliadin. Levels of these antibodies were not found to be increased in individuals with schizophrenia compared with controls [142].

Autism spectrum disorders

Autism Spectrum Disorders (ASDs) have been linked with GI symptoms in several studies. Children with ASD experience a higher rate of GI symptoms than controls [143] and 40-60% of ASD children suffer from GI problems [144]. Children with more severe autism are likely to have more severe GI symptoms, and children with more severe GI symptoms are more likely to have more severe autism [145].

Asperger [146] discussed a possible link between Asperger Syndrome and CD more than a half century ago. Subsequently, Goodwin and Goodwin [147] hypothesized a possible association between autism and gluten in their case report of child with autism who demonstrated improvement following the initiation of a GFD. Return to a normal diet resulted in an exacerbation of autistic symptoms [148]. Subsequently, several additional studies described a link between autism and CD [149-153]. However, other studies found no association between these disorders [154,155].

Several studies describe increased intestinal permeability in ASD [156-158], but not all confirm this finding [158]. Individuals with ASD have also been demonstrated to have increased permeability to food antigens containing gliadin [159] along with altered blood brain barrier (BBB) integrity [160].

Investigators have reported improvement in ASD symptoms following the introduction of a GFD [161-166]. However, others report minimal, if any, correlation between ASD symptoms and changes in dietary gluten [167-171]. One author suggested a subset of individuals with autism might benefit from a GFD [172], but thus far the symptoms or testing profile of these individuals remains unclear.

A possible link between ASD and antibodies commonly found in CD has been reported. Individuals with serological markers for CD but normal mucosa were found to be three times more likely to develop autism in the future [173]. The authors of this study suggested these individuals might suffer from non-celiac gluten sensitivity (NCGS) rather than CD. Levels of anti-gliadin IgG and anti-deamidated gliadin IgG have been reported to be elevated in individuals with ASD compared with controls [159,174]. Anti-gliadin IgG levels were significantly higher in children with ASD who also reported GI symptoms than in those without GI symptoms. The levels of antibodies to deamidated gliadin and tTG2 did not differ between individuals with CD and controls [174].

Eating disorders

Nearly a century after Anorexia Nervosa was first described [175], CD was reported to occur in association with eating disorders (ED) [176]. Numerous case reports describe ED co-occurring with CD [176-182]. In addition, several clinical studies have examined the link between ED and CD. Findings from these studies include an increase in altered or disordered eating behavior in CD patients compared with healthy controls [183-185] and a higher than expected rate of ED in adolescents with CD [186].

In a study examining the personality characteristics of female adolescents with CD, individuals with CD and a comorbid ED were found to be older, had a higher current BMI, higher maximum BMI, higher depression scores, and more dietary transgressions than individuals with CD but no ED. The authors concluded that adolescents with CD should be monitored for BMI, dietary transgressions, personality factors, and depressive symptoms [187].

Not all studies support a positive association between CD and ED's, however. The authors of a review of psychiatric disorders in CD surmised it is unclear whether a causal link exists between eating disorders and CD [95]. A prospective study of 154 children and adolescents with ED found none who suffered from CD [188]. A retrospective chart review of 494 patients who had been evaluated for an ED and screened for CD found 10 (2%) who tested positive for anti-tTG antibodies. Of those individuals, 4 had biopsy confirmed CD *via* endoscopy for an overall prevalence rate of 0.8%. Given that this prevalence rate is similar to the rate found in the general population, the authors suggested routine screening of individuals with EDs for CD is not indicated [189]. In a similar study, 177 individuals with anorexia nervosa were screened for CD by checking levels of serum IgA and IgG to tTG. The prevalence rate of CD was found to be similar to that observed in the general population [190].

Pica has been reported to occur in association with CD, although descriptions are limited to case studies [191-193]. Iron deficiency has been proposed as one cause of pica, and iron deficiency may occur in CD as a result of malabsorption. The complete resolution of pica was reported in 3 children with comorbid CD and pica following the introduction of a GFD [191].

In summary, although the connection between CD and EDs remains controversial, it is clear that an incorrect diagnosis of an

ED can obscure a correct diagnosis of CD [181,194] and CD can produce disordered eating behavior [195]. Clinicians should remain vigilant to the possibility of underlying CD when a patient presents with symptoms of an ED, and should explore the possibility of disordered eating behavior in patients with CD. At this time, there is insufficient evidence to support routine screening of individuals with ED for CD.

Attention-deficit/hyperactivity disorder (ADHD)

An association between Attention-Deficit/Hyperactivity Disorder (ADHD) and CD has been reported. A retrospective study found ADHD-like symptomatology was "over represented" in 132 individuals with untreated CD compared to the general population [196]. These symptoms improved following 6-months on a GFD. The majority (74%) of individuals wanted to continue the GFD following the study due to significant relief of their symptoms [196]. This study lacked a control group, however.

A subsequent study measured levels of anti-gliadin antibodies (AGA) and anti-endomysium (ESA) antibodies in 67 individuals with ADHD. Ten of the 67 individuals were found to be positive for these antibodies. Furthermore, subjects and their parents reported significant improvement in behavior and functioning following six months on a GFD [197].

Not all studies support the finding of a positive association between CD and ADHD, however. In a Turkish study, serum levels of IgA and IgG to tTG were evaluated in 362 children and adolescents who met DSM-IV-TR criteria for ADHD. Seropositive subjects then underwent endoscopic duodenal biopsy. Seropositive rates were similar in the ADHD and control groups [198].

In a recent review, eight studies reporting an association between CD and ADHD were evaluated. Inconsistent results were found with only three studies reporting a positive correlation between CD and ADHD. The authors found insufficient evidence to support routine screening of ADHD patients for CD (or vice versa) or institution of a GFD in ADHD [199].

Discussion

Studies examining an association between CD and comorbid psychiatric disorders are fraught with numerous limitations. These include: disparities in study design, small sample size, lack of controls, differing diagnostic criteria, varying levels of psychopathology between the randomized groups, inconsistent status on a GFD, different lengths of treatment, dissimilar outcome measures, disparate ages of subjects, and variable assessment for the presence of serological markers associated with CD [200,201]. Despite these limitations, evidence exists to support an association between CD and psychiatric disorders, even if only in a subset of CD patients.

Numerous pathophysiological mechanisms have been proposed to explain the association between CD and psychiatric disorders. These include: toxic effects of gluten, an autoimmune reaction triggered by gluten, psychological reactions to the physical symptoms of CD resulting in behavioral changes [187],

elevated production of nitric oxide, and malabsorption syndromes resulting in deficiencies of tryptophan, thiamine (Vitamin B1), pyridoxine (Vitamin B6), folic acid (Vitamin B9), and cyanocobalamin (Vitamin B12).

Given the high rate of unrecognized CD in the general population [13], a high index of suspicion is required to identify psychiatric patients who may be suffering from undiagnosed CD. Also, in psychiatric patients who are resistant to traditional therapeutic interventions, a diagnosis of CD should be considered if symptoms of CD are present or if a positive family history of CD exists. By understanding the myriad clinical presentations of CD, clinicians can better identify patients who are appropriate candidates for serological screening for CD, thus improving the chances of a positive clinical outcome.

Based upon World Health Organization criteria, Fasano recommended mass screening for CD. Other authors have recommended genetic screening for at-risk infants. Given the increasing prevalence of CD, the difficulty diagnosing this condition based upon varying clinical presentations, and the possible absence of symptoms, we feel it is important for clinicians to be aware of the possibility of CD in patients with psychiatric conditions and consider ordering serological tests (e.g., anti-tTG antibodies) as part of the diagnostic work up in patients who present with psychiatric disorders known to co-occur with CD. However, studies examining the prevalence of CD in psychiatric disorders have provided inconsistent results. Therefore, we do not recommend screening all psychiatric patients for CD.

Additional studies are needed to further explore the relationship between psychiatric disorders and CD. Elevated antibody levels found to co-occur in CD and certain psychiatric disorders provide a clue that may lead to a better understanding of common pathophysiological mechanisms and result in new treatments for psychiatric conditions. Furthermore, additional investigations into the effects of CD on the blood brain barrier are needed.

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