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CELIAC DISEASE AND BIPOLAR DISORDER: THE POTENTIAL ROLE OF THE GUT-BRAIN AXIS

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ABSTRACT

Introduction: Celiac disease is a chronic autoimmune enteropathy triggered by gluten ingestion in genetically predisposed individuals. Beyond its digestive manifestations, it can be accompanied by numerous extra-digestive manifestations, particularly neurological and psychiatric ones. Among these, the association with bipolar disorder remains rare and insufficiently documented, although several recent studies suggest a role for immune dysregulation, chronic inflammation, and the gut-brain axis in this association.

Case report: We report the case of a 60-year-old patient followed since the age of 21 for celiac disease, confirmed by positive anti-transglutaminase antibodies and duodenal biopsy. Seven years after diagnosis, she experienced a first manic episode in the context of bereavement, leading to a diagnosis of type I bipolar disorder. Her clinical course was marked by several manic and depressive episodes requiring both outpatient and inpatient management, while her celiac disease remained controlled under a strict gluten-free diet and regular gastroenterological follow-up.

Discussion: Data from the literature report an increased frequency of mood disorders among patients with celiac disease. Several pathophysiological mechanisms have been proposed to explain this association, including chronic immune activation, production of pro-inflammatory cytokines, increased intestinal permeability, alterations of the gut microbiota, and nutritional deficiencies secondary to malabsorption. Our observation is consistent with these data and highlights the value of a multidisciplinary approach in the management of these patients.

Conclusion: This case illustrates a rare association between celiac disease and type I bipolar disorder. Although a causal link cannot be established, it underscores the importance of clinical vigilance regarding the emergence of psychiatric symptoms in patients with celiac disease, and encourages prospective studies to better understand the underlying pathophysiological mechanisms.

KEYWORDS: celiac disease; bipolar disorder; gut-brain axis; inflammation; autoimmunity; case report.

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by gluten ingestion in genetically predisposed individuals, mainly carriers of the HLA-DQ2 and HLA-DQ8 haplotypes (1). It is characterized by chronic inflammation of the small intestinal mucosa, resulting in villous atrophy and malabsorption of numerous nutrients. Its prevalence is estimated at approximately 1% of the global population, with a female predominance (2). Although the classic digestive manifestations, such as chronic diarrhea, weight loss, and abdominal pain, remain the best-known forms, extra-digestive presentations are now widely recognized and are sometimes the presenting feature of the disease (3).

Over the past decades, growing interest has been directed toward the neurological and psychiatric manifestations of celiac disease. Indeed, several studies have reported a higher frequency of psychiatric disorders in patients with this condition compared with the general population (4,5). Among the most frequently observed disorders are anxiety disorders, depressive episodes, eating disorders, autism spectrum disorders, and certain psychotic disorders (6). More recently, several studies have also suggested an association between celiac disease and bipolar disorder, although this relationship remains insufficiently understood (7).

Bipolar disorder is a chronic psychiatric condition characterized by alternating manic, hypomanic, and depressive episodes, interspersed with periods of euthymia. It represents one of the leading causes of disability in young adults and is associated with substantial functional morbidity as well as a high risk of suicide (8,9). While its etiopathogenesis remains multifactorial, involving genetic, neurobiological, and environmental factors, recent data highlight the potential role of immune-inflammatory mechanisms in its development and course (10).

The association between celiac disease and bipolar disorder is of particular interest because of potentially shared pathophysiological mechanisms. Several hypotheses have been proposed, including chronic activation of the immune system, production of pro-inflammatory cytokines, increased intestinal permeability, alterations of the gut microbiota, nutritional deficiencies secondary to malabsorption, and the existence of a gut-brain axis playing a major role in the regulation of neuropsychiatric functions (11). These mechanisms could contribute to the onset or worsening of mood disorders in some patients with celiac disease.

Furthermore, several observational studies have shown that patients with celiac disease have a higher prevalence of mood disorders (7), while elevated concentrations of anti-gliadin antibodies have been found in some patients with bipolar disorder, particularly during manic episodes (12,13). Although current data do not allow a causal link to be established, they reinforce the hypothesis of a complex interaction between immune dysregulation, systemic inflammation, and psychiatric vulnerability.

In this context, the reporting of clinical cases remains essential to better characterize this association, which is still rare in the literature. We report the case of a patient followed for several decades for biologically and histologically confirmed celiac disease, who subsequently developed type I bipolar disorder, marked by several manic and depressive episodes. Through this case report, we present a narrative review of the literature on the links between celiac disease and bipolar disorder, discussing the main pathophysiological hypotheses as well as the diagnostic and therapeutic implications of this association.

CASE REPORT

A 60-year-old patient, single, working as a schoolteacher, was followed for celiac disease diagnosed at the age of 21. The diagnosis had been established on the basis of a clinical picture combining chronic diarrhea, significant weight loss, and hypochromic microcytic anemia resistant to iron therapy. Immunological work-up had revealed positive anti-transglutaminase antibodies, and duodenal biopsy confirmed the diagnosis by showing villous atrophy consistent with celiac disease. A strict gluten-free diet was then initiated, along with regular gastroenterological follow-up.

At the age of 28, in the context of bereavement following her father's death, the patient presented a first manic episode characterized by elevated mood, decreased need for sleep, pressured speech, increased psychomotor activity, grandiose ideas, and behavioral disinhibition. The clinical course was favorable under treatment combining an antipsychotic

and a mood stabilizer, with complete remission of symptoms and a return to her previous level of functioning, leading to a diagnosis of type I bipolar disorder.

Over the course of her illness, several manic and depressive episodes occurred successively, requiring management alternating between outpatient follow-up and hospitalization depending on the severity of the mood decompensations. Two hospitalizations in particular took place at the Ar-razi University Psychiatric Hospital in Salé. Between episodes, the patient regained a satisfactory level of functioning, allowing her to continue her professional activity.

At the same time, gastroenterological follow-up was continued on a regular basis, with an annual consultation combined with clinical and biological monitoring. The patient reported good adherence to the gluten-free diet, with a favorable digestive course and no complications related to celiac disease.

At the most recent evaluation, her psychiatric condition was stable under treatment with a mood stabilizer combined with an antipsychotic, with no acute mood symptoms. From a somatic standpoint, her celiac disease continued to show a satisfactory course under the gluten-free diet.

This case highlights the coexistence of celiac disease evolving over several decades and type I bipolar disorder that developed secondarily. It raises the question of potential interactions between these two conditions, particularly through immune-inflammatory mechanisms and the gut-brain axis, which will be discussed in light of recent data from the literature.

DISCUSSION

4.1. Association between celiac disease and bipolar disorder: data from the literature

Celiac disease is now recognized as a systemic condition whose manifestations extend well beyond the digestive tract. In addition to nutritional, bone, and autoimmune complications, several studies have shown an increased frequency of neurological and psychiatric manifestations in patients with this condition (3). Anxiety and depressive disorders are the most frequently reported, but a growing number of studies also suggest an association with bipolar disorder, although this relationship remains insufficiently elucidated (6).

The earliest data supporting this association came from serological studies showing an increased prevalence of antibodies against gluten in patients with bipolar disorder. In a case-control study published in 2011, Dickerson and colleagues compared 102 patients with bipolar disorder to 173 controls with no psychiatric history (12). The authors observed a significantly higher frequency of IgG anti-gliadin antibodies in patients with bipolar disorder,

suggesting an abnormal immune response to gluten in this population. These findings led to the hypothesis that gluten sensitivity might affect a subgroup of patients with bipolar disorder.

The following year, the same authors conducted a prospective study of 60 patients hospitalized for an acute manic episode (14). They showed that IgG anti-gliadin antibody concentrations were significantly elevated during the manic phase, and that patients who still had elevated levels six months after hospitalization had a higher risk of relapse. This observation suggests that gluten-related immune activation may be associated with disease activity rather than being a simple incidental comorbidity.

Other studies have examined the prevalence of bipolar disorder in patients with celiac disease. In a case-control study published in 2015, Carta and colleagues compared 60 patients with celiac disease to 240 control subjects (7). The authors reported a significantly higher prevalence of bipolar disorder in the celiac disease group (4.3% versus 0.4%), reinforcing the hypothesis of an association between the two conditions.

More recently, Alkhayyat and colleagues analyzed data from 360 American hospitals between 2016 and 2020 (15). This large-scale study confirmed that patients with celiac disease had an increased risk of developing several psychiatric disorders, including bipolar disorder. These findings provide an additional level of evidence supporting a population-level association between the two conditions.

Our observation is consistent with this body of evidence. In our patient, celiac disease had been diagnosed several years before the onset of type I bipolar disorder. Although a causal link cannot be established from a single clinical case, this chronology is consistent with data from the literature suggesting that the immune and inflammatory abnormalities associated with celiac disease may contribute, in predisposed individuals, to the emergence of mood disorders.

However, the data currently available remain limited. Most studies are observational, involve relatively small sample sizes, or mainly assess serological markers of gluten sensitivity rather than histologically confirmed celiac disease. In addition, confounding factors such as shared genetic predispositions, associated autoimmune diseases, or nutritional deficiencies make it difficult to establish a causal relationship. Prospective, multicenter studies using standardized diagnostic criteria are still needed to clarify the exact nature of this association.

4.2. Pathophysiological mechanisms explaining the association between celiac disease and bipolar disorder

The pathophysiological mechanisms linking celiac disease to bipolar disorder remain incompletely understood. However, recent advances in neuroimmunology have made it possible to identify several biological pathways that could explain this association (10,11). The main hypotheses are based on immune dysregulation, chronic inflammation, impairment of the intestinal barrier, alterations of the gut microbiota, and nutritional deficiencies secondary to malabsorption.

4.2.1. Immune dysregulation and chronic inflammation

Celiac disease is characterized by abnormal activation of the adaptive immune response in the presence of gluten in genetically predisposed individuals. This activation leads to substantial production of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interferon gamma (IFN-γ), which are responsible for intestinal mucosal damage (1).

At the same time, numerous studies have shown that bipolar disorder is also associated with a state of chronic low-grade inflammation. Manic and depressive episodes are frequently accompanied by increased circulating concentrations of pro-inflammatory cytokines (16), suggesting that immune system activation participates in the pathophysiological mechanisms of the disorder (10). This systemic inflammation could promote changes in neurotransmission, brain metabolism, and neuronal plasticity, thereby contributing to the onset of mood disorders.

The existence of this shared inflammatory signature constitutes one of the strongest hypotheses explaining the increased frequency of bipolar disorder in patients with celiac disease.

4.2.2. Impairment of the intestinal barrier and the gut-brain axis

The gut-brain axis represents a complex network of bidirectional communication linking the digestive tract to the central nervous system through immune, endocrine, metabolic, and neuronal mechanisms (11).

In celiac disease, exposure to gluten leads to increased intestinal permeability, sometimes referred to as « leaky gut » (17). This impairment of the intestinal barrier facilitates the passage of gluten-derived peptides, bacterial lipopolysaccharides, and inflammatory mediators into the systemic circulation. These molecules can activate peripheral immune cells, disrupt the integrity of the blood-brain barrier, and induce neuroinflammation.

This persistent immune activation could alter the functioning of brain networks involved in mood regulation, thereby promoting the onset or exacerbation of mood episodes in vulnerable individuals.

4.2.3. Intestinal dysbiosis

The gut microbiota plays a major role in maintaining immune homeostasis and in communication between the gut and the brain. Several studies have shown that celiac disease is accompanied by dysbiosis characterized by a decrease in protective commensal bacteria and an increase in certain potentially pro-inflammatory species (18).

Comparable changes in the microbiota have also been described in patients with bipolar disorder (11). This dysbiosis could influence the synthesis of numerous neuroactive metabolites, including short-chain fatty acids, tryptophan, serotonin, and gamma-aminobutyric acid (GABA), which are involved in the regulation of emotions and behavior. Although the data remain preliminary, the gut microbiota is now emerging as a potential player in the pathophysiology of bipolar disorder.

4.2.4. Nutritional deficiencies

The chronic malabsorption observed in celiac disease can lead to deficiencies in iron, vitamin B12, folate, and vitamin D (19), several of which are involved in brain function.

These deficiencies can disrupt neurotransmitter synthesis, promote oxidative stress, and impair neuronal methylation mechanisms. They have been associated with an increased risk of depressive disorders, chronic fatigue, and cognitive impairment. In some patients, they may also contribute to the mood instability observed in bipolar disorder, although their exact role remains to be clarified.

4.2.5. Genetic predisposition and autoimmunity

Celiac disease occurs preferentially in individuals carrying the HLA-DQ2 and HLA-DQ8 haplotypes, reflecting the importance of genetic factors in its pathogenesis (2). Although no shared genetic determinant has been clearly identified with bipolar disorder, several authors suggest that certain immunogenetic profiles could simultaneously predispose individuals to autoimmune diseases and psychiatric disorders.

Furthermore, patients with bipolar disorder have a higher frequency of autoimmune diseases than the general population (20), which reinforces the hypothesis of shared immunological susceptibility. This convergence of genetic factors, immune dysregulation, and chronic inflammation could contribute to the concomitant development of these two conditions.

In our case, celiac disease preceded the onset of bipolar disorder by several years. Although this chronological sequence does not establish a causal relationship, it is consistent with the

pathophysiological hypotheses currently proposed. The combination of persistent immune activation, chronic systemic inflammation, and alteration of the gut-brain axis may have created a favorable environment for the emergence of bipolar disorder in this genetically predisposed patient.

4.3. Diagnostic and therapeutic implications

The association between celiac disease and bipolar disorder, although rare, raises several practical implications in terms of screening, management, and multidisciplinary follow-up. Currently available data suggest that psychiatric manifestations may precede, accompany, or follow the diagnosis of celiac disease, making their early recognition particularly important.

In patients with celiac disease, the occurrence of persistent or atypical psychiatric symptoms, particularly recurrent mood episodes, should prompt a specialized psychiatric evaluation. Conversely, in patients with bipolar disorder associated with chronic digestive symptoms, unexplained iron-deficiency anemia, weight loss, nutritional deficiencies, or a family history of autoimmune diseases, screening for celiac disease should be considered. Measurement of IgA anti-transglutaminase antibodies, together with total IgA levels, constitutes the first-line test, with diagnosis confirmed by duodenal biopsy in cases of positive serology (21).

Management of these patients should be based on a multidisciplinary approach involving psychiatrists, gastroenterologists, and nutritionists. This collaboration not only ensures optimal control of both conditions but also helps prevent complications related to nutritional deficiencies, improve treatment adherence, and optimize patients' quality of life.

The strict gluten-free diet remains the reference treatment for celiac disease. Beyond its efficacy on digestive symptoms and intestinal mucosal healing (21), several studies have reported improvement in certain neuropsychiatric symptoms after its initiation. A reduction in anxiety and depressive symptoms, improved cognitive performance, and better quality of life have been described in some adherent patients (22). In contrast, evidence regarding its effectiveness on the course of bipolar disorder remains limited. To date, no controlled study has demonstrated that a gluten-free diet can prevent manic or depressive relapses in patients with bipolar disorder. Available data are mainly based on clinical observations and case series, which does not allow for specific recommendations to be made.

In the case presented, celiac disease was diagnosed several years before the onset of bipolar disorder and was managed with regular gastroenterological follow-up, with good adherence to the gluten-free diet. Despite this management, several mood episodes occurred during the course of the illness, requiring appropriate psychotropic treatment. This observation

highlights that adherence to the gluten-free diet, although essential for controlling celiac disease, does not by itself constitute a sufficient strategy to prevent the onset or recurrence of bipolar disorder. Psychiatric management should therefore continue to follow international guidelines, while taking into account the specific features related to the underlying autoimmune disease.

Ultimately, this association highlights the importance of a comprehensive approach to patient care. A better understanding of the interactions between immunity, inflammation, and brain function could, in the future, pave the way for new diagnostic and therapeutic strategies targeting the pathophysiological mechanisms shared by both conditions.

4.4. Limitations and perspectives

This case report has several points of interest. First, it describes an uncommon association between biologically and histologically confirmed celiac disease and type I bipolar disorder, two conditions whose pathophysiological links remain incompletely understood. The long duration of clinical follow-up also makes it possible to trace the chronological course of both conditions, with celiac disease preceding the onset of bipolar disorder by several years. This timeline is consistent with the pathophysiological hypotheses reported in the literature, particularly those involving chronic inflammation, immune dysregulation, and the gut-brain axis.

Furthermore, this observation is compared with the main data from the literature, making it possible to place the patient's clinical characteristics in perspective with current knowledge. This approach helps strengthen the educational and clinical value of this work by raising clinicians' awareness of an association that is probably underdiagnosed.

Nevertheless, several limitations should be noted. As with any clinical case, this observation does not allow a causal relationship to be established between celiac disease and bipolar disorder. The absence of assessment of certain inflammatory, immunological, or microbiological biomarkers also limits the exploration of the pathophysiological mechanisms that may link these two conditions. Likewise, it was not possible to objectively assess the impact of the gluten-free diet on the course of mood symptoms during follow-up.

Despite these limitations, this observation provides additional support for the existence of complex interactions between autoimmune diseases and mood disorders. It underscores the need for further research, particularly through prospective, multicenter studies, to better understand the mechanisms involved and to identify patients who may benefit from integrated care.

CONCLUSION

The association between celiac disease and bipolar disorder remains rare and still insufficiently characterized. However, recent data from the literature, together with the case presented here, suggest the existence of complex interactions involving immune dysregulation, chronic inflammation, alteration of the gut-brain axis, and changes in the gut microbiota. Although a causal link cannot be established at this time, these mechanisms represent plausible pathophysiological pathways that may contribute to the onset of mood disorders in some patients with celiac disease.

This case underscores the importance of a multidisciplinary approach involving psychiatrists, gastroenterologists, and nutritionists to ensure comprehensive patient care. Particular vigilance is recommended for the emergence of psychiatric symptoms in patients with celiac disease, as is targeted screening for this condition in patients with bipolar disorder associated with digestive signs, unexplained nutritional deficiencies, or a personal or family history of autoimmune diseases.

Prospective, multicenter studies based on immunological and inflammatory biomarkers are now needed to better understand the mechanisms linking these two conditions and to evaluate the value of targeted therapeutic strategies in this population.

REFERENCES

1. Lebwohl B, Sanders DS, Green PHR. Celiac disease : a comprehensive current review. BMC Med. 2019 ;17 :142.
2. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global prevalence of celiac disease : systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018 ;16(6) :823-836.
3. Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. Psychiatr Q. 2012 ;83(1) :91-102.
4. Butwicka A, Lichtenstein P, Frisén L, Almqvist C, Larsson H, Ludvigsson JF. Celiac disease is associated with childhood psychiatric disorders : a population-based study. J Pediatr. 2017 ;184 :87-93.
5. Lebwohl B, Haggård L, Emilsson L, Söderling J, Roelstraete B, Butwicka A, et al. Psychiatric disorders in patients with a diagnosis of celiac disease during childhood, 1973-2016 : a nationwide cohort study. Clin Gastroenterol Hepatol. 2021 ;19(2) :375-383.

6. Slim M, Rico-Villademoros F, Calandre EP. Psychiatric comorbidity in children and adults with gluten-related disorders : a narrative review. Nutrients. 2018 ;10(7) :875.
7. Carta MG, Conti A, Lecca F, Sancassiani F, Cossu G, Carruxi R, et al. The burden of depressive and bipolar disorders in celiac disease. Clin Pract Epidemiol Ment Health. 2015 ;11 :180-185.
8. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011 ;68(3) :241-251.
9. Dome P, Rihmer Z, Gonda X. Suicide risk in bipolar disorder : a brief review. Medicina (Kaunas). 2019 ;55(8) :403.
10. Rosenblat JD, McIntyre RS. Bipolar disorder and immune dysfunction : epidemiological findings, proposed pathophysiology and clinical implications. Brain Sci. 2017 ;7(11) :144.
11. Obi-Azuike C, Ebiai R, Gibson T, Hernandez A, Khan A, Anugwom G, et al. A systematic review on gut-brain axis aberrations in bipolar disorder and methods of balancing the gut microbiota. Brain Behav. 2023 ;13(6) :e3037.
12. Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Alaedini A, et al. Markers of gluten sensitivity and celiac disease in bipolar disorder. Bipolar Disord. 2011 ;13(1) :52-58.
13. Porcelli B, Verdino V, Ferretti F, Bizzaro N, Terzuoli L, Cinci F, et al. A study on the association of mood disorders and gluten-related diseases. Psychiatry Res. 2018 ;260 :366-370.
14. Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R. Markers of gluten sensitivity in acute mania : a longitudinal study. Psychiatry Res. 2012 ;196(1) :68-71.
15. Alkhayyat M, Qapaja T, Aggarwal M, Almomani A, Abureesh M, Al-otoom O, et al. Epidemiology and risk of psychiatric disorders among patients with celiac disease : a population-based national study. J Gastroenterol Hepatol. 2021 ;36(8) :2165-2170.
16. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder : a meta-analysis of 30 studies. Biol Psychiatry. 2013 ;74(1) :15-25.
17. Fasano A. Leaky gut and autoimmune diseases. Clin Rev Allergy Immunol. 2012 ;42(1) :71-78.
18. Girbovan A, Sur G, Samasca G, Lupan I. Dysbiosis a risk factor for celiac disease. Med Microbiol Immunol. 2017 ;206(2) :83-91.

19. Wierdsma NJ, van Bokhorst-de van der Schueren MAE, Berkenpas M, Mulder CJ, van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. Nutrients. 2013 ;5(10) :3975-3992.
20. Wang LY, Chiang JH, Chen SF, Shen YC. Systemic autoimmune diseases are associated with an increased risk of bipolar disorder : a nationwide population-based cohort study. J Affect Disord. 2018 ;227 :31-37.
21. Rubio-Tapia A, Hill ID, Semrad C, Kelly CP, Greer KB, Limketkai BN, Lebwohl B. American College of Gastroenterology guidelines update : diagnosis and management of celiac disease. Am J Gastroenterol. 2023 ;118(1) :59-76.
22. Addolorato G, Capristo E, Ghittoni G, Valeri C, Mascianà R, Ancona C, Gasbarrini G. Anxiety but not depression decreases in coeliac patients after one-year gluten-free diet : a longitudinal study. Scand J Gastroenterol. 2001 ;36(5) :502-506.