Original Article

Markers of gluten sensitivity and celiac disease in bipolar disorder

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Alaedini A, Yolken R. Markers of gluten sensitivity and celiac disease in bipolar disorder.
Bipolar Disord 2011: 13: 52–58. © 2011 The Authors.
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Objectives: Increased immune sensitivity to dietary gluten proteins has been reported in schizophrenia but has not been studied in bipolar disorder. In this study, we examine the levels of antibody reactivity to gliadin, deamidated gliadin, and tissue transglutaminase (tTG) in individuals with bipolar disorder and compare these levels to those in individuals who do not have any history of psychiatric disorder.

Methods: The sample of 275 individuals included 102 with bipolar disorder and 173 controls without a psychiatric disorder. Immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to gliadin and tTG and IgG antibodies to deamidated gliadin were measured by enzyme immunoassay. Participants' levels of antibodies to deamidated gliadin and tTG were classified based on the cutoffs for positivity that are predictive of celiac disease. Quantitative levels of antibodies were compared between groups employing regression models which were controlled for demographic variables.

Results: Individuals with bipolar disorder had increased levels of IgG antibodies to gliadin compared with controls in multivariate analyses. We also found evidence of increased levels of antibodies to deamidated gliadin in the bipolar disorder population. The levels of IgA class antigliadin antibodies and antibodies to tTG did not differ significantly between groups. There was also not a significant difference between groups in the number of persons who were classified as having levels of antibodies to deamidated gliadin or tTG that are predictive of celiac disease.

Conclusions: Individuals with bipolar disorder have increased levels of IgG antibodies to gliadin. However, such antibody increase is not accompanied by an elevation in IgA antibodies to gliadin or the celiac disease-associated antibodies against deamidated gliadin and tTG. These results warrant further detailed examination of the molecular specificity and pattern of reactivity of the antibody response to gluten antigens in bipolar disorder.

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Bipolar disorder is a serious mental illness of unknown etiology. Immunological abnormalities have been identified and may contribute to the pathophysiology of the disorder in some individuals (1, 2). Increased immune sensitivity to gluten is one type of immunologic abnormality which has been previously described in schizophrenia (3–6) but which has not been studied in bipolar disorder.

Glutens, which include gliadins and glutenins, are the main storage proteins of wheat and are comprised of more than 100 different species with similar amino acid sequences and biochemical properties (1). Gluten sensitivity may be defined as a state of heightened immune response to ingested gluten (7).

The most widely recognized clinical manifestation of gluten sensitivity is celiac disease, an inflammatory enteropathy that is characterized by villous atrophy and lymphocytic infiltration in the small intestine in genetically predisposed individuals (2). Celiac disease is closely associated genetically with class II human leukocyte antigens (HLA)-DQ2 and -DQ8, as well as antibodies to specific deamidated epitopes of gliadin and to tissue transglutaminase (tTG) enzyme (7, 8). Gluten sensitivity has also been reported to be associated with several extraintestinal manifestations, including specific neurologic and psychiatric deficits, such as peripheral neuropathy, cerebellar ataxia, and schizophrenia (3–5).

In investigations of gluten sensitivity in schizophrenia, some studies have found an association between schizophrenia and celiac disease (9–11), while others have not (12–14). In a previous study, we found that individuals with a recent onset of psychosis had increased levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to gliadin compared with controls, and that individuals with multi-episode schizophrenia also had significantly increased levels of IgG antibodies to gliadin (3). However, the levels of IgG antibodies to deamidated gliadin and IgA antibodies to tTG were not elevated in either psychiatric group. We also found in another previous study of individuals with schizophrenia that the antibody response to gliadin differed in terms of antigen specificity from that of celiac disease patients and was not associated with HLA-DQ2 and -DQ8 markers (15). These findings suggested that the immune response to gliadin in schizophrenia involves a mechanism that is different from that of individuals with celiac disease, being independent of the action of the tTG enzyme and HLA-DQ2/DQ8 molecules.

In this study, we examine the levels of antibody reactivity to gliadin, deamidated gliadin, and tTG in individuals with bipolar disorder and compare them to those in individuals who do not have any history of psychiatric disorder.

Methods

The study population consisted of 275 individuals: 102 with a diagnosis of bipolar disorder and 173 controls without a history of psychiatric disorder. Individuals with bipolar disorder were recruited from outpatient and inpatient programs affiliated with a large psychiatric health system and from other outpatient treatment sites in the region. Their diagnosis was confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)–Patient Edition (16), based on the DSM-IV (17), and with available medical records.

Individuals without a history of psychiatric disorder were recruited by posted announcements at local health care facilities and universities in the same geographic area as the sites from which the individuals with bipolar disorder were drawn. The controls were enrolled after they were screened with the SCID–Non-patient Edition (18) to rule out a current or past psychiatric disorder. All participants from the bipolar disorder group and the control group met the following additional criteria: age 18–65; and absence of any history of intravenous substance abuse, mental retardation, or serious medical disorder that would affect cognitive functioning. A further criterion for the bipolar disorder participants was the absence of a primary diagnosis of alcohol or substance use disorder within the past three months. Information on gastrointestinal symptoms was obtained from individuals with bipolar disorder by means of interview. For the purposes of analysis, significant gastrointestinal symptoms included diarrhea, lactose intolerance, constipation, or irritable bowel syndrome. Participants in either the case or control groups were not selected or excluded based on gastrointestinal symptoms or a history of celiac disease.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and the Johns Hopkins Medical Institutions following established guidelines. All participants provided written informed consent after the study procedures were explained.

A blood sample was obtained at the study visit for all participants. Serum IgG and IgA class antibodies to gliadin, IgG and IgA class antibodies to tTG, and IgG class antibodies to deamidated gliadin were measured by commercially available solid phase immunoassays (obtained from IBL International Gmbh, Hamburg, and Orgentec Diagnostika, Mainz, Germany). IgG class antibodies to deamidated gliadin were measured by a commercially available solid phase immunoassay (Quanta Lite Gliadin IgG II, Inova Diagnostics, San Diego, CA, USA). To allow for the comparison of antibody levels across the different assays, all results were expressed in standardized units where the mean level of antibody in the control population was set as 1.0 U, following previously

described procedures (3). We measured the HLA-DQ2 and -DQ8 genotypes using real-time polymerase chain reaction (19). Adequate DNA samples for these analyses were available from 39 individuals with bipolar disorder and 169 controls.

Participants were asked about their educational level and other demographic variables, as well their smoking status. All participants were individually administered a brief cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status, Form A (RBANS) (20). Participants in the bipolar disorder group were also interviewed and rated on the Positive and Negative Syndrome Scale (PANSS) (21), the Young Mania Rating Scale (22), and the Hamilton Depression Rating Scale (23) to assess current psychiatric symptoms; participants were also asked questions to determine whether or not they had a history of psychotic symptoms. Psychiatric medication data were recorded from participant self-report or clinical charts, and it was noted whether or not each patient was receiving any of the following types of medication at the time of the study visit: lithium, anticonvulsant mood stabilizer, atypical antipsychotic, or antidepressant medication.

Statistical analyses

The levels of IgG and IgA antibodies to gliadin, IgG antibody to deamidated gliadin, and IgG and IgA antibodies to tTG in individuals with bipolar disorder and in control participants were initially compared by Kruskal–Wallis nonparametric analysis of variance; this method of analysis was used because the antibody levels were not normally distributed.

In the case of the assays for IgG and IgA antibodies to tTG and IgG antibodies to deamidated gliadin, samples were also categorically classified as being abnormal as defined by being above the assigned cutoff value (which was determined from the reactivity of standard samples provided by the manufacturer).

We employed regression models to determine the association of the antibodies with clinical status, controlling for the demographic variables of age, gender, race (black versus non-black), and maternal education. Continuous levels were compared employing the nonparametric method of interquartile regression following the imputation of missing data. Logistic regression models were employed to determine the odds ratios (OR) associated with elevated levels of antibodies to each of the antigens, defined as $\geq 75^{th}$ percentile measured in the control population. For these analyses, a critical value of $p < 0.01$ was employed to denote statistical significance in light of testing for five antibodies. Any p-values between 0.01 and 0.05 were considered to be suggestive in light of the multiple comparisons.

Within the group of individuals with bipolar disorder, we employed Kruskal–Wallis analysis of variance and Spearman rank correlation analyses to examine the relationship between IgG class antibodies to gliadin and the following clinical characteristics: PANSS total symptom score, Young Mania Rating Scale score, Hamilton Depression Rating Scale score, RBANS total cognitive score, the presence of gastrointestinal symptoms, current smoking status, use of specific types of psychiatric medication, and history of psychotic symptoms. All statistical analyses were performed with STATA version 11 (College Station, TX, USA).

Results

Sample characteristics

The demographic and clinical characteristics of the study populations are presented in Table 1. The two groups differed significantly when compared on age and race. The groups did not differ significantly in gender distribution or level of maternal education. Within the bipolar disorder group, participants had the following diagnoses: (i) bipolar I disorder, most recent episode manic [(n = 25), 25%]; (ii) bipolar I disorder, most recent episode depressed [(n = 40), 40%]; (iii) bipolar I disorder, most recent episode mixed [(n = 16), 16%]; (iv) bipolar disorder not otherwise specified (NOS) [(n = 1), 1%]; and (v) bipolar II disorder [(n = 20), 20%]. All but 3 persons in the bipolar disorder group were receiving psychotropic medication at the time of the study assessment. Duration of mood disorder among bipolar disorder participants was an average of 20.0 years

Table 1. Demographic and clinical characteristics of the study populations

	Bipolar disorder (n = 102)	Nonpsychiatric controls (n = 173)
Age, years, mean (SD)[a]	39.5 (12.4)	32.0 (11.2)
Gender, male, n (%)	32 (31)	48 (28)
Race, n (%)[b]		
Caucasian	78 (76)	103 (60)
African American	19 (19)	57 (33)
Other	5 (5)	13 (8)
Maternal education, years, mean (SD)	12.9 (3.1)	13.6 (3.0)

[a]$\chi^2 = 24.2$, $p < 0.0001$.
[b]$\chi^2 = 8.2$, $p < 0.02$.

(SD = 12.0), and 74 (73%) had a history of psychotic symptoms. At the time of the assessment, 86 (84%) were receiving an anticonvulsant mood stabilizer or lithium and 29 (28%) were receiving lithium; 48 (47%) were receiving an atypical antipsychotic; and 57 (56%) were receiving an antidepressant.

Antibody levels

The distribution of IgG antibodies to gliadin in individuals with bipolar disorder and controls is depicted in Figure 1. The bipolar disorder group had significantly elevated levels of IgG antibodies to gliadin when compared to the nonpsychiatric controls (χ^2 = 15.8, p < 0.0001, Kruskal–Wallis analysis of variance). The groups did not differ significantly in unadjusted levels of IgA antibodies to gliadin, IgG antibodies to deamidated gliadin, or IgA and IgG antibodies to tTG (all p > 0.05).

Because the bipolar disorder group differed from the control group in terms of a number of demographic variables, we employed nonparametric regression models to define the independent relationship between the bipolar disorder group and antibody levels. As depicted in Table 2, the levels of IgG antibody to gliadin in the bipolar disorder group were found to be significantly different from those of the control group independent of age, gender, race, or maternal education (coefficient = 0.54, t = 6.45, p < 0.0001). Employing a similar regression model, the level of

IgG antibodies to deamidated gliadin displayed a suggestive association with bipolar disorder diagnosis independent of age, gender, race, or maternal education (coefficient = 0.63, t = 2.29, p = 0.023). On the other hand, no significant associations were found between bipolar disorder and IgA antibodies to gliadin or IgG and IgA antibodies to tTG. None of the antibody levels displayed independent associations with the demographic variables of age, gender, race, or maternal education (all p > 0.05).

We also employed logistic regression models to determine the ORs associated with elevated levels of antibodies to each of the antigens, defined as ≥ 75th percentile of antibodies measured in the control population. As shown in Table 3, we found that the individuals with bipolar disorder had significantly increased odds of having elevated levels of IgG class antibodies to gliadin using the 75th percentile cutoff [OR = 2.52, 95% confidence interval (CI): 1.44–4.39; p = 0.001]. There were no independent associations between elevated levels of IgG antibodies to gliadin and age, race, gender, or maternal education. We also found that the individuals with bipolar disorder had significantly increased odds of having elevated levels of antibodies to deamidated gliadin (OR = 2.24, 95% CI: 1.27–3.97; p = 0.005). Elevated levels of antibody to deamidated gliadin displayed a suggestive association with decreased age (OR = 0.97, 95% CI: 0.95–1.00, p = 0.026) but were not significantly associated with gender, race, or maternal
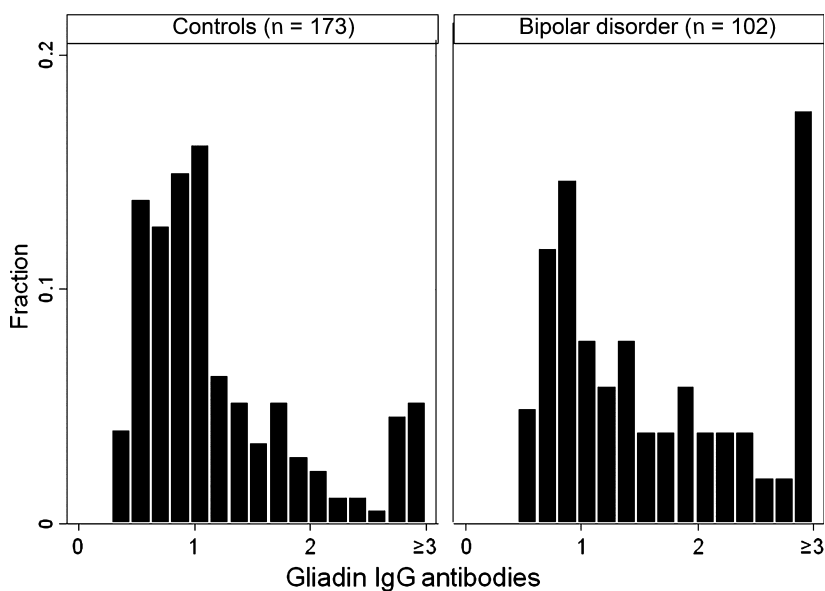

Fig. 1. Distribution of antibodies to immunoglobulin G (IgG) gliadin in the bipolar disorder and nonpsychiatric disorder comparison group. The y-axis represents the fraction of individuals in the indicated diagnostic category. The x-axis indicates the levels of antibody in arbitrary units with the median of the controls equal to 1.

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Table 2. Comparison of markers of gluten sensitivity and celiac disease in individuals with bipolar disorder (n = 102) compared to nonpsychiatric controls (n = 173) by interquartile regression model

Dependent variable	Coefficient	95% CI	p-value
IgA antibodies to gliadin[a]	0.062	−0.121–0.245	0.505
IgG antibodies to gliadin[b]	0.542	0.377–0.701	< 0.0001
IgG antibodies to deamidated gliadin[c]	0.063	0.009–0.118	0.023
IgA antibodies to tTG[d]	0.005	−0.050–0.061	0.842
IgG antibodies to tTG[e]	0.048	−0.051–0.147	0.341

The nonpsychiatric control group is the reference group; all analyses include the covariates of age, gender, race, and maternal education. IgA = immunoglobulin A; IgG = immunoglobulin G; tTG = tissue transglutaminase; CI = confidence interval.
[a]Overall equation, $F = 0.96$, $p = 0.442$.
[b]Overall equation, $F = 5.46$, $p < 0.0001$.
[c]Overall equation, $F = 1.98$, $p = 0.082$.
[d]Overall equation, $F = 0.91$, $p = 0.478$.
[e]Overall equation, $F = 1.26$, $p = 0.283$.

Table 3. Comparison of markers of gluten sensitivity and celiac disease in individuals with bipolar disorder (n = 102) compared to nonpsychiatric controls (n = 173) by logistic regression models

Dependent variable	OR[a]	95% CI	p-value
IgA antibodies to gliadin[b]	1.04	0.56–1.93	0.912
IgG antibodies to gliadin[c]	2.52	1.44–4.39	0.001
IgG antibodies to deamidated gliadin[d]	2.24	1.27–3.97	0.005
IgA antibodies to tTG[e]	1.36	0.77–2.42	0.285
IgG antibodies to tTG[f]	1.15	0.65–2.04	0.634

IgA = immunoglobulin A; IgG = immunoglobulin G; tTG = tissue transglutaminase; OR = odds ratio; CI = confidence interval.
[a]ORs calculated on the basis of being ≥ 75th percentile of the control population.
[b]Overall equation, $F = 0.72$, $p = 0.609$.
[c]Overall equation, $F = 2.55$, $p = 0.026$.
[d]Overall equation, $F = 2.43$, $p = 0.033$.
[e]Overall equation, $F = 1.43$, $p = 0.212$.
[f]Overall equation, $F = 0.44$, $p = 0.821$.

education. Individuals with bipolar disorder did not have significant independent associations with IgA class antibodies to gliadin or with IgA and IgG class antibodies to tTG.

We also determined how many individuals had levels of antibodies to deamidated gliadin predictive of celiac disease based on cutoff values set by the manufacturer of the test kits employed for these measurements. Such levels of antibody to deamidated gliadin were found in 4 of 102 individuals with bipolar disorder and 1 of 192 control individuals (p = 0.065, Fisher's exact test). Levels of IgA antibodies to tTG predictive of celiac

disease were found in one individual with bipolar disorder and in no controls; levels of IgG antibodies to tTG were found in 9 (8.8%) individuals with bipolar disorder and in 7 (4.1%) control individuals. These differences were not statistically significant.

We also examined the relationship between IgG class antibodies to gliadin and to deamidated gliadin and clinical characteristics within the bipolar disorder group. Levels of antibodies did not correlate with PANSS total symptom score, Young Mania Rating Scale score, Hamilton Depression Rating Scale score, RBANS total cognitive score, the presence of gastrointestinal symptoms, current smoking status, use of specific psychiatric medications, or a history of psychotic symptoms (all p > 0.1).

DNA samples were available from 39 individuals with bipolar disorder and 169 controls for determination of HLA-DQ2 and -DQ8 genotypes. A total of 18/39 (46.2%) in the bipolar disorder sample and 47/169 (27.8%) among the controls had DQ2 or DQ8 (p = 0.07, logistic regression adjusted for race, gender, and level of maternal education). There were no significant associations between the observed increased antibody reactivity to any of the gliadin or tTG antibodies and these genotypes in individuals with bipolar disorder (p > 0.1).

Discussion

Our study documents that individuals with bipolar disorder have increased levels of IgG class antibodies to gliadin as compared to control individuals without a history of psychiatric disorder. These increases in antigliadin antibody levels are independent of demographic factors such as age, gender, race, and maternal education.

Increased antibody response to gliadin is a hallmark of celiac disease, a multisystem autoimmune disease associated with structural and functional alterations in the gastrointestinal tract (24, 25). However, the profile of antibody reactivity to other celiac disease-associated markers in our study population of bipolar disorder patients differed from that found in individuals with celiac disease. The levels of IgG and IgA antibodies to tTG, which are highly specific for celiac disease, were not elevated in the bipolar disorder group in comparison to the nonpsychiatric control group (26). In addition, while > 85% of celiac disease patients have antibodies to deamidated gliadin (15, 27, 28), only a small minority of bipolar disorder patients had a level of these antibodies that exceeded the level set by the kit manufacturer.

On the other hand, we did find some evidence of increased levels of antibodies to deamidated gliadin in comparison to the nonpsychiatric control group.

The results of this study are of interest in light of our earlier study of gluten sensitivity in recent-onset psychosis and multi-episode schizophrenia (3). In both studies, we found significantly elevated levels of IgG antibodies to gliadin in the psychiatric groups as compared to nonpsychiatric controls. However, while the recent-onset psychosis group displayed elevated IgA antibody to gliadin, such association was not found in multi-episode schizophrenia and bipolar disorder groups. Similarly, while marginally elevated levels of IgG antibody to tTG were found in recent-onset psychosis, no such increase was seen in the bipolar disorder or schizophrenia groups. On the other hand, the suggestive association of antideamidated gliadin antibody with bipolar disorder diagnosis was not found for recent-onset psychosis or multi-episode schizophrenia. The functional and biological significance of these antibodies should be the subject of future investigations.

It is likely that the individuals with bipolar disorder who have increased antibodies to gliadin share some pathobiological features of celiac disease, such as abnormal absorption of ingested food proteins, a finding which is also consistent with the increased levels of antibodies to bovine casein which have also been found in bipolar disorder (29) as well as recent-onset psychosis and schizophrenia (30). In addition, immune abnormalities stemming from genetic predisposition or environmental factors might also play a significant role in the form of B cell and effector cell dysregulation that leads to elevated levels of antibodies to certain dietary proteins (6). However, the mechanism of the increased antibody response to gluten is likely to be different in bipolar disorder in comparison to celiac disease. Considering the observed antibody profile in bipolar disorder, we may conclude that the elevated antigliadin antibody response in affected patients is independent of the enzymatic action of tTG and does not require presentation of gluten peptides to T cells by the celiac disease-associated HLA-DQ2 and -DQ8 molecules. As with schizophrenia, in which a distinct pattern of reactivity to gluten has been found, the molecular specificity of the antigliadin antibody response in patients with bipolar disorder may also differ from that in celiac disease patients (15).

Our finding of increased levels of antibodies to gliadin in individuals with bipolar disorder as well as in individuals with recent-onset psychosis and schizophrenia suggests that this immune abnormality is not specific to one diagnostic group within serious mental illness. However, there might be differences in the specificity of the antibody response toward the various gluten proteins in these diseases. Delineation of such differences may be helpful in developing biomarkers for the identification of specific disease phenotypes, while yielding new insights about the role of the immune system in specific mental disorders. Thus, these results warrant further detailed examination of the molecular specificity and pattern of reactivity of the antibody response to gluten antigens in recent-onset psychosis, schizophrenia, and bipolar disorder patients. At this point, it remains to be determined whether gluten proteins or the observed elevated immune response to them have any role in the pathogenic mechanism of bipolar disorder or have the potential to serve as biomarkers of disease diagnosis or activity. While a gluten-free diet has been reported to be effective in some cases of schizophrenia, controlled studies have not been carried out for any group of patients with neuropsychiatric disorders. Thus, future work should also focus on the effect of dietary exclusion of gluten in patients with elevated antibodies in carefully devised, controlled trials, as well as in longitudinal studies aimed at determining the timing of the relationship between antibody response to gluten antigens and disease course. Further elucidation of the relationship between the immune response to gluten and onset of disease may lead to new methods of treatment in some individuals with bipolar disorder and other serious mental illnesses.

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