Markers of Gluten Sensitivity and Celiac Disease in Recent-Onset Psychosis and Multi-Episode Schizophrenia

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Background: Increased immune sensitivity to gluten has been reported in schizophrenia. However, studies are inconsistent about this association.

Methods: The sample of 471 individuals included 129 with recent-onset psychosis, 191 with multi-episode schizophrenia, and 151 controls. Immunoglobulin (Ig)G and IgA antibodies to gliadin and to tissue transglutaminase, and IgG antibodies to deamidated gliadin were measured. Quantitative levels of antibodies in the psychiatric groups were compared with controls. All participants were categorized as to whether their levels of antibodies met standardized cutoffs for celiac disease. HLA DQ2 and HLA DQ8 alleles were detected by real-time polymerase chain reaction.

Results: Individuals with recent-onset psychosis had increased levels of IgG (odds ratio [OR] 5.50; 95% confidence interval [CI] 2.65–11.42) and IgA (OR 2.75; 95% CI 1.31–5.75) antibodies to gliadin compared with control subjects. Individuals with multi-episode schizophrenia also had significantly increased levels of IgG antibodies to gliadin (OR 6.19; 95% CI 2.70–14.16). IgG antibodies to deamidated gliadin and IgA antibodies to tissue transglutaminase were not elevated in either psychiatric group, and fewer than 1% of individuals in each of the groups had levels of these antibodies predictive of celiac disease. There were no significant differences in the distribution of the HLA DQ2/8 alleles among the groups.

Conclusions: Individuals with recent-onset psychosis and with multi-episode schizophrenia who have increased antibodies to gliadin may share some immunologic features of celiac disease, but their immune response to gliadin differs from that of celiac disease.

Key Words: Antibody, celiac disease, gliadin, immunity, psychosis, schizophrenia

Schizophrenia is a disease of unknown etiology. Immunologic 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 that has been previously described (3–6).

Glutens, which include gliadins and glutenins, are the main storage proteins of wheat and comprise more than 100 species with similar amino acid sequences and biochemical properties (7). Gluten sensitivity may be defined as a state of heightened immune response to ingested gluten. Many individuals with gluten sensitivity also develop celiac disease, an inflammatory enteropathy that is characterized by villous atrophy and lymphocytic infiltration in the small intestine in genetically predisposed individuals (8,9). Celiac disease is associated with increased reactivity to the epitopes present in deamidated forms of gluten (10) as well as to tissue transglutaminase (9). Most individuals with celiac disease also have defined HLA DQ genotypes that contribute to disease pathogenesis by modulating the immune response to ingested glutens (11).

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The results of studies looking at the association between schizophrenia and celiac disease have been mixed. Some studies have found an increased co-occurrence of the two disorders (12–14), but other studies have not found an association (15–17). In a previous study, we found that 17 individuals with schizophrenia who had elevated immunoglobulin (Ig)G and IgA antibodies to gliadin had immune responses that differed from that of individuals with celiac disease (18). In this study, we examine the levels of antibody reactivity to gliadin, deamidated gliadin, and tissue transglutaminase in a large group of individuals with recent-onset psychosis and individuals with multi-episode schizophrenia and compare these reactivities to those in individuals who do not have any history of psychiatric disorder.

Methods and Materials

The study population consisted of 471 individuals: 129 with a recent onset of psychosis; 191 with multi-episode schizophrenia, not of recent onset (referred to from here on as the "schizophrenia" group); and 151 controls without a history of psychiatric disorder. The details of the recruitment and evaluation of individuals in these populations have been previously described (19–21). The recent-onset psychosis sample met the following criteria: onset of psychotic symptoms for the first time within the previous 24 months defined as the presence of a positive psychotic symptom of at least moderate severity that lasted through the day for several days or occurred several times a week and could not have been limited to a few brief moments, aged between 13 and 45 inclusive, voluntary admission status if hospitalized, and absence of substance-induced psychosis or of psychotic symptoms that occurred only in the context of intoxication or withdrawal. All the recent-onset patients were receiving antipsychotic medication at the time of study participation. The individuals with schizophrenia met the following criteria: aged

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between 18 and 65 inclusive, diagnosis of schizophrenia or schizoaffective disorder meeting criteria in the DSM-IV (22), onset of psychotic symptoms more than 24 months earlier, and currently receiving antipsychotic medication treatment. The nonpsychiatric control sample met the following criteria: aged between 18 and 65 inclusive and absence of a current or past psychiatric disorder as confirmed by screening with the Structured Clinical Interview for DSM-IV Axis I Disorders—Nonpatient Edition (23). All participants from the patient groups and the control group met the following additional criteria: absence of current substance dependence over the previous 1 month and of any history of intravenous substance abuse, absence of mental retardation, and absence of serious medical disorder that would affect cognitive functioning. Information about gastrointestinal symptoms was obtained from individuals with recent-onset psychosis or multi-episode schizophrenia by means of interview. For the purposes of analysis, significant gastrointestinal symptoms included diarrhea, lactose intolerances, 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 participants with recent-onset psychosis were recruited from inpatient and day hospital programs at a large psychiatric health system. The participants with schizophrenia were recruited from psychiatric programs affiliated with the same psychiatric health system and at other outpatient treatment sites in the region. The control individuals without a history of psychiatric disorder were recruited from posted announcements at local health care facilities and universities in the same geographic area as the sites where the individuals with recent-onset psychosis and those with schizophrenia were drawn.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and 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 and IgG and IgA class antibodies to tissue transglutaminase and IgG class antibodies to deamidated gliadin were measured by commercially available solid phase immunoassays (obtained from IBL International, Hamburg Germany, and Organetec Diagnostica, 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, California). To allow for the comparison of antibody levels across the different assays, all results were expressed in standardized units in which the mean level of antibody in the control population was set as 1.0 U, following previously described procedures (19). The presence of HLA DQ2 and HLA DQ8 alleles were measured by real-time polymerase chain reaction as previously described (24). Participants were asked about their educational level and other demographic variables as well as the presence of co-occurring medical conditions. All participants were individually administered a brief cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Form A) (25). Participants in the patient psychiatric groups were also interviewed and rated on the Positive and Negative Syndrome Scale (26) to assess current psychiatric symptoms; medication data were recorded from their clinical charts.

Statistical Analyses

The levels of gliadin IgA, gliadin IgG, deamidated gliadin IgG, atissue transglutaminase IgA, and tissue transglutaminase IgG antibodies of the individuals with recent-onset psychosis and schizophrenia and control subjects were initially compared by one-way analysis of variance. Quantitative levels of antibodies were also compared using linear regression models employing the covariates of age, sex, race, maternal education (as a proxy for socioeconomic status), and current smoking status. Imputations were performed for missing data using previously described methods (27).

We employed logistic regression models with the covariates to calculate the odds ratios associated with increased levels of antibodies in the individuals with recent-onset psychosis and those with multi-episode schizophrenia. For these analyses, increased levels of antibodies were defined as antibody levels at 90th percentile or higher of the control subjects as previously described (19). In the case of the assays for tissue transglutaminase IgA and deamidated gliadin IgG, samples were also categorically classified as being above or below the reaction of standard samples provided by the manufacturer containing approximately 10 U of antibody, a level considered highly associated with the presence of celiac disease (28).

A critical p value $< .01$ was employed to denote statistical significance in light of testing for five antibodies; p values between .01 and .05 were considered suggestive in light of the multiple comparisons.

We also examined the relationship between IgG class antibodies to gliadin and clinical and demographic characteristics within the groups of individuals with recent-onset psychosis or multi-episode schizophrenia by linear regression analysis with the covariates noted earlier.

All statistical analyses were performed with Stata (version 11, College Station, Texas).

Results

Sample Characteristics

The demographic and clinical characteristics of the study populations are presented in Table 1. Within the recent-onset group, participants had the following diagnoses: schizophreniform disorder (n = 20, 16%); schizophrenia (n = 19, 15%); schizoaffective disorder (n = 13, 10%); bipolar I disorder, most recent episode manic (n = 18, 14%); bipolar I disorder, most recent episode depressed (n = 9, 7%); bipolar I disorder, most recent episode mixed (n = 9, 7%); bipolar disorder single manic episode (n = 4, 3%); major depression with psychotic features (n = 22, 17%); bipolar II disorder (n = 2, 2%); delusional disorder (n = 2, 2%); brief reactive psychosis (n = 2, 2%); and psychotic disorder not otherwise specified (n = 9, 7%). Within the schizophrenia group, the patients had the following diagnoses: paranoid subtype (n = 52, 27%), undifferentiated subtype (n = 44, 23%), schizoaffective disorder (n = 87, 46%), other schizophrenia subtype (n = 8, 4%).

All persons in the psychiatric groups were receiving psychotropic medication at the time of the study assessment. The following medications were the most commonly received: olanzapine, n = 27 (21%) of the recent-onset and n = 53 (28%) of the schizophrenia group; risperidone n = 52 (40%) of the recent-onset and n = 49 (26%) of the schizophrenia group; clozapine, n = 3 (2%) of the recent-onset and n = 40 (21%) of the schizophrenia group; lithium, n = 26 (20%) of the recent-onset and n = 21 (11%) of the schizophrenia group; quetiapine, n = 16

Table 1. Demographic and Clinical Characteristics of Study Populations

	Recent-Onset Psychosis (n = 129)	Multi-Episode Schizophrenia (n = 191)	Nonpsychiatric Control Subjects (n = 151)
	Mean (SD) or n (%)		
Age, years	24.9 (7.8)	43.5 (10.3)	32.8 (11.7)
Sex, male	67 (52%)	111 (58%)	40 (26%)
Race			
Caucasian	78 (60%)	95 (50%)	83 (55%)
African American	42 (33%)	93 (49%)	56 (37%)
Other	9 (7%)	3 (1%)	12 (8%)
Years Education	13.0 (3.1)	11.9 (2.5)	15.3 (2.0)
Years Maternal Education[a]	13.7 (2.6)	12.4 (2.9)	13.5 (3.1)
Duration of Illness, Years[b]	.5 (.6)	22.1 (10.3)	—
Current Cigarette Smoker	42 (28%)	126 (66%)	32 (22%)

[a] n = 124 for the recent onset of psychosis group; n = 153 for the multi-episode schizophrenia group, and n = 150 for the controls.
[b] n = 187 for the multi-episode schizophrenia group.

(12%) of the recent-onset and n = 29 (15%) of the schizophrenia group; haloperidol, 8 (6%) of the recent-onset and 32 (17%) of the schizophrenia group; ziprasidone, 10 (8%) of the recent-onset and 15 (8%) of the schizophrenia group; and valproate, 18 (14%) of the recent-onset and 37 (20%) of the schizophrenia group. The HLA DQ2 and/or DQ8 alleles were detected in 36.8% of the individuals with recent-onset psychosis and 32.4% of the individuals with multi-episode schizophrenia. These levels did not differ from the 33.8% of individuals in the control group who had these alleles ($p > .05$).

Table 3. Comparison of Markers of Gluten Sensitivity and Celiac Disease in Individuals with Recent Onset Psychosis (n = 129), Multi-episode Schizophrenia (n = 191), and Nonpsychiatric Controls (n = 151) by Linear Regression Model[a]

Dependent Variable	Coefficient	95% Confidence Interval	p Value[b]
IgA Antibodies to Gliadin[c]			
Recent-onset psychosis	.567	.282 to 851	<.0001
Multi-episode schizophrenia	.278	−.007 to .563	.056
IgG Antibodies to Gliadin[d]			
Recent-onset psychosis	1.16	.855 to 1.449	<.0001
Multi-episode schizophrenia	.542	.251 to .833	<.0001
Antibodies to Deamidated Gliadin[e]			
Recent-onset psychosis	.007	−165 to .179	.937
Multi-episode schizophrenia	.071	−.098 to .240	.409
IgA Antibodies to Tissue Transglutaminase[f]			
Recent-onset psychosis	.122	−.062 to .307	.193
Multi-episode schizophrenia	.015	−.167 to .196	.874
IgG Antibodies to Tissue Transglutaminase[g]			
Recent-onset psychosis	.244	.035 to .455	.023
Multi-episode schizophrenia	.080	−.127 to .286	.449

Ig, immunoglobulin.
[a] The nonpsychiatric control group is the reference group; all analyses include the covariates of age, sex, race, maternal education, and current smoking status.
[b] Cutoff for significance = $p < .01$ to adjust for multiple comparisons.
[c] Overall equation, $F(6, 211.6) = 4.37$, $p = .0004$.
[d] Overall equation, $F(6, 449.5) = 11.98$, $p < .0001$.
[e] Overall equation, $F(6,455) = 1.51$, $p = .173$.
[f] Overall equation, $F(6, 219.3) = .71$, $p = .640$.
[g] Overall equation, $F(6, 461.9) = 1.43$, $p = .201$.

Antibody Levels

As shown in Table 2, the three groups differ significantly in their levels of IgA and IgG antibodies to gliadin and also IgG antibodies to tissue transglutaminase in unadjusted comparisons. There were no significant differences among the groups in their levels of IgG class antibodies to deamidated gliadin or to IgA tissue transglutaminase.

We then examined the relationship between clinical diagnosis and levels of antibodies to gliadin and tissue transglutaminase by multivariate analysis as depicted in Table 3. The linear regression models employed age, sex, race, maternal education, and current cigarette smoking as covariates. We found that individuals with a recent onset of psychosis had increased levels of IgG class ($p = < .0001$) and IgA class ($p = < .0001$) antibodies to gliadin compared with control subjects. By contrast, we did not find any increase in the levels of IgG antibodies to deamidated gliadin or IgA class antibodies to tissue transglutaminase. We found suggestive levels of IgG class antibodies to tissue transglutaminase ($p = .023$), but these were not considered significant in light of the multiple comparisons. We also found that individuals with multi-episode schizophrenia had increased levels of IgG class antibodies to gliadin ($p < .0001$). However, these individuals did not have significantly increased levels of IgA antibodies to gliadin nor increased levels of IgG class antibodies to deamidated gliadin or increased levels of IgG or IgA class antibodies to tissue transglutaminase.

We also employed logistic regression models to determine the odds ratios associated with elevated levels of antibodies to each

Table 2. Mean Levels of Markers of Gluten Sensitivity and Celiac Disease in Study Populations[a]

	Recent-Onset Psychosis (n = 129)	Multi-Episode Schizophrenia, (n = 191)	Nonpsychiatric Controls (n = 151)	Test Statistic and p Value
	Mean (SD)			
IgG Antibodies to Gliadin	2.17 (1.77)	1.40 (1.03)	1.0 (.61)	$F = 35.03$ ($p = < .0001$)
IgA Antibodies to Gliadin	1.48 (1.20)	1.38 (1.21)	1.0 (.64)	$F = 7.59$ ($p = .0006$)
Antibodies to Deamidated Gliadin	1.04 (.74)	1.01 (.68)	1.0 (.67)	$F = .015$ ($p = .857$)
IgA Antibodies to Tissue Transglutaminase	1.13 (.64)	1.07 (1.00)	1.0 (.27)	$F = 1.06$ ($p = .347$)
IgG Antibodies to Tissue Transglutaminase	1.24 (.82)	1.04 (.71)	1.0 (.74)	$F = 4.08$ ($p = .017$)

Ig, immunoglobulin.
[a] Mean level of the control group = 1; one-way analysis of variance among groups.

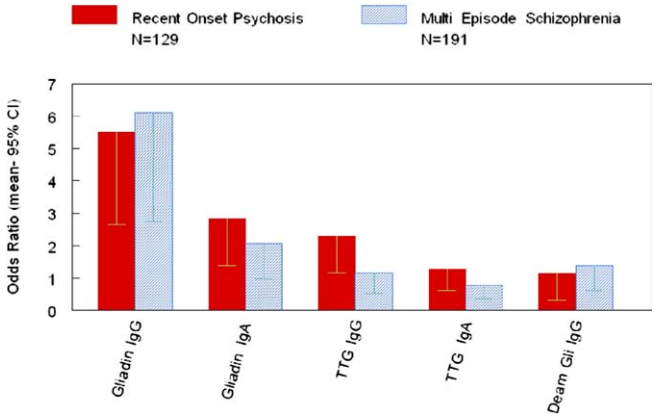

Figure 1. Odds ratios associated with increased levels of antibodies to gliadin and tissue transglutaminase (TTG) in individuals with recent-onset psychosis ($n = 129$) and multi-episode schizophrenia ($n = 191$) compared with nonpsychiatric controls ($n = 151$). All analyses are adjusted for age, sex, race, maternal education, and current smoking status. CI, confidence interval; IgA, immunoglobulin A; IgG, immunoglobulin G.

of the antigens, defined as ≥ 90th percentile of antibodies measured in the control population as shown in Figure 1. We found that individuals with recent-onset psychosis had increased odds of having elevated levels of IgG class antibodies to gliadin (odds ratio [OR] 5.50; 95% confidence interval [CI] 2.65–11.42) and statistically significant but lower odds of having elevated levels of IgA class antibodies to gliadin, OR = 2.75; 95% CI 1.31–5.75). Individuals with recent onset of psychosis had marginally increased odds of having elevated levels of IgG class antibodies to tissue transglutaminase (OR 2.29; 95% CI 1.15–4.55) but did not have evidence of elevated levels of IgA class antibodies to tissue transglutaminase or IgG class antibodies to deamidated gliadin. Individuals with multi-episode schizophrenia also had increased odds of having elevated IgG class antibodies to gliadin (OR 6.19, 95% CI 2.70–14.16), but not of having elevated levels of antibodies to the other antigens.

We also determined how many individuals had levels of tissue transglutaminase IgA or deamidated gliadin IgG antibodies predictive of celiac disease based on cutoff values set by the manufacturer. Such levels of antibodies to tissue transglutaminase IgA were found in 1 of the 191 individuals (.5%) with multi-episode schizophrenia and 1 of the 129 individuals with a recent onset of psychosis (.8%) and in no control individuals. We did not find levels of antibodies to deamidated gliadin in any of the individuals with multi-episode schizophrenia or recent-onset psychosis; such levels of antibodies were found in 1 (.7%) of the 151 control individuals.

We also examined the relationship between IgG class antibodies to gliadin and clinical and demographic characteristics within the groups of individuals with recent-onset psychosis or multi-episode schizophrenia. Levels of antibodies were not associated with age, sex, race, or level of maternal education. Similarly levels of antibodies did not correlate with Positive and Negative Syndrome Scale total symptom score, RBANS total cognitive score, the presence of gastrointestinal symptoms, use of specific psychiatric medications, or the presence of the HLA DQ2/8 haplotypes (all $p > .05$).

Discussion

Our study documents that individuals with a recent onset of psychosis have increased levels of IgG and IgA class antibodies to gliadin compared with control individuals without a history of psychiatric disorder. Individuals with multi-episode schizophrenia, not of recent onset, also have increased levels of antigliadin antibodies compared with control subjects, although their levels of antibodies are lower than those found in individuals with recent-onset psychosis. These increases in antibody levels are independent of demographic factors that might be associated with antibodies to gliadin such as age, sex, race, maternal education, and cigarette smoking status.

Increases in antibodies to gliadin are found in individuals with celiac disease, which is a multisystem autoimmune disease associated with structural and functional alterations in the gastrointestinal tract (9). However, the immunologic pattern measured in our study population differed somewhat from that found in individuals with celiac disease. For example, we found that individuals with recent-onset psychosis or multi-episode schizophrenia did not have increased levels of IgG antibodies to deamidated gliadin or IgA antibodies to tissue transglutaminase, both of which are found in most individuals with celiac disease (29,30). Individuals with recent-onset psychosis did have marginal increases in IgG class antibodies to tissue transglutaminase; however, individuals with multi-episode schizophrenia did not have any evidence of increased levels of these antibodies. In addition, fewer than 1% of individuals in each of the three groups had levels of IgA antibodies to tissue transglutaminase or IgG antibodies to deamidated gliadin; these are the antibodies that are considered most specific for the presence of celiac disease (28). Furthermore, we did not find disease-related differences in the prevalence of HLA DQ2/8 alleles that are found in most individuals with celiac disease. We did not perform additional assays that have been previously used for the evaluation of celiac disease, such as the measurement of antibodies to endomysium, because the antibody panel we used has been found to detect virtually all cases of celiac disease (31). It is of note that we found marginal increased in IgG class antibodies to tissue transglutaminase in the group of individuals with the recent onset of psychosis. Such antibodies have been found in some individuals undergoing an infectious process in the absence of celiac disease (32). This finding is thus consistent with previous studies indicating that individuals with the recent onset of psychosis have evidence of increased rates of respiratory and other infections compared with control populations (19,33).

The results of this study are consistent with our previous research indicating that individuals with schizophrenia recognize epitopes on gliadin molecules but that the antigenic epitopes recognized differ from those recognized by individuals with celiac disease (18). Our studies are also consistent with previous studies indicating that individuals with schizophrenia have increased levels of antibodies to gliadin (4–6). However, our findings are also consistent with studies indicating that individuals with recent-onset psychosis or multi-episode schizophrenia do not have clinical manifestations of celiac disease nor laboratory parameters which are diagnostic of this disorder (15–18).

It is likely that the individuals with recent-onset psychosis and schizophrenia 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 this population (34). However, the lack of increased levels of IgG antibodies to deamidated gliadin and IgA antibodies to tissue transglutaminase suggests that the immune response to gliadin in individuals with recent-onset psychosis and schizophrenia differs from that of

individuals with celiac disease, perhaps because of the lack of celiac disease–related genes in the HLA DQ complex.

Our finding of increased levels of antibodies to gliadin in individuals with the recent onset of psychosis suggests that the immune pathological abnormalities associated with these antibodies are present early in the course of disease. Furthermore, individuals with recent-onset psychosis had higher levels of IgA class antibodies to gliadin compared with individuals with multiepisode schizophrenia, not of recent onset. The biological meaning of the differential response between IgG and IgA antibodies to gliadin is not known with certainty but may be related to differences in terms of timing and site of exposure. These possible mechanisms should be the subject of future investigation. Because of the cross-sectional nature of our study, we could not measure the time course of the development of gliadin antibodies and the development of the symptoms of psychosis or schizophrenia. Longitudinal studies should be employed to study this relationship. In addition, it is unknown whether elevated levels of antibodies to gliadin are also found in persons with other psychiatric disorders—for example, persons with nonpsychotic bipolar disorder; this topic should be the focus of future investigation. Furthermore, we could not determine whether the antibodies to gliadin contribute directly to the symptoms of recent-onset psychosis or schizophrenia. This possibility should be examined by prospective studies as well as by studies directed at lowering the level of antibodies to gliadin by means of dietary interventions. If successful, such studies might lead to new methods for the treatment of symptoms in some individuals with recent-onset psychosis and schizophrenia.

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