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Gluten sensitivity and relationship to psychiatric symptoms in people with schizophrenia

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Abstract

The relationship between gluten sensitivity and schizophrenia has been of increasing interest and novel mechanisms explaining this relationship continue to be described. Our study in 100 people with schizophrenia compared to 100 matched controls replicates a higher prevalence of gluten sensitivity and higher mean antigliadin IgG antibody levels schizophrenia (2.9 ± 7.7 vs. 1.3 ± 1.3, p = 0.046, controlled for age). Additionally, we examined symptoms within the schizophrenia group and found that while positive symptoms are significantly lower in people who have elevated antigliadin antibodies (AGA; 4.11 ± 1.36 vs. 6.39 ± 2.99, p = 0.020), no robust clinical profile

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Conflict of interest

Dr. Fasano is co-founder and stockholder in Alba Therapeutics. Dr. McMahon was a statistical consultant for Amgen. All other authors declare that they have no conflicts of interest.

Contributors

Dr. Kelly designed the study and contributed to the data analysis, writing and final manuscript. Ms. Jackson was involved with the study design and wrote the first manuscript draft. Dr. McMahon provided statistical support and helped with the final draft. Dr. Fasano, Dr. Eaton, Dr. Carpenter, and Dr. Cascella were involved with the study design and writing the final manuscript. Dr. Santora performed lab assays on the participant samples, assisted with the study design and with the final draft. Ms. Sullivan and Ms. Raley participated in the study design, collected patient data and helped with the final draft. Ms. Feldman contributed to the study design, data collection, and final manuscript.

differentiates between positive and negative antibody groups. Thus, identifying people in schizophrenia who may benefit from a gluten-free diet remains possible by blood test only.

Keywords

Gluten; Celiac disease; Schizophrenia; Gliadin; Gluten sensitivity

1. Introduction

Celiac disease (CD) is an autoimmune disease involving the adaptive immune system and permeability of the intestine. Gluten sensitivity (GS) involves the innate immune system, and little or no pathology in the intestine (Jackson et al., 2012b). Accumulating evidence suggests a relationship between gluten-related disorders, including GS and autoimmune CD, to mental illness and neurologic disease. A wide range of diseases including autism (de Magistris et al., 2010); (Lau et al., 2013), epilepsy (Hernandez et al., 1998; Antigoni et al., 2007), ataxia (Luostarinen et al., 2001; Hadjivassiliou et al., 2003), anxiety (Addolorato et al., 1996); (Hauser et al., 2010), and depression (Addolorato et al., 1996); (Hauser et al., 2010) have been implicated. Psychosis has been of particular interest, with five studies showing an association of schizophrenia of non-affective psychosis with GS (Okusaga et al., 2013); (Dickerson et al., 2010); (Reichelt and Landmark, 1995); (Dohan et al., 1972); (Cascella et al., 2011) and two others showing a relationship with bipolar disease or mania (Dickerson et al., 2012a); (Dickerson et al., 2012b). In the largest study, 23.1% and 5.4% of persons with schizophrenia had elevated IgA antigliadin antibodies (AGA) (indicative of GS) and tissue transglutaminase antibodies (tTG) (suggestive of CD), compared to elevated AGA and tTG present in only 3.3 and 1.1% of controls samples, respectively (Cascella et al., 2011). An increased association between schizophrenia and CD in particular (Eaton et al., 2004) and autoimmune diseases in general has been documented as well (Eaton et al., 2006; Chen et al., 2012).

Recent data suggests that immune mechanisms related to gluten exposure mediate the occurrence of the associated psychiatric and neurologic symptoms in genetically susceptible individuals. For example, CD patients on a gluten-free diet (GFD) and without neurological symptoms may have white matter hyperintensities in frontal and occipitoparietal cortices and gray matter reduction in the cortex and caudate nucleus (Bilgic et al., 2013). Multiple sclerosis and associated white matter abnormalities also have been demonstrated in people with CD (Batur-Caglayan et al., 2013). Brain hypoperfusion has been demonstrated in people with CD with improvement on a GFD (Addolorato et al., 2004). Moreover, people with CD who are not on a GFD demonstrate IgA antibodies to brain blood vessels (Pratesi et al., 1998). Cytotoxicity may also be an important mechanism of brain damage in patients with either GS or CD. In a case report, a patient with gluten ataxia and dementia had infiltration of CD8+ and perforin and granzyme B-expressing cells as well as microglial activation in damaged brain areas (Mittelbronn et al., 2010).

Gastrointestinal inflammation, possibly from infection by a number of agents, is increased in people with schizophrenia and may allow food antigens to activate the immune system (Severance et al., 2012). In one study the risk of nonaffective psychosis was elevated in

children of women expressing high levels of AGA–IgG, which cross the placenta: the authors suggested that inflammation associated with this process may cause damage in the developing fetus (Karlsson et al., 2012). Thus, interactions between the immune system and the central nervous system may contribute to the development of schizophrenia in people with gluten-related disorders through injury from the antibodies to gluten or ensuing immune-related mechanisms.

GS in schizophrenia has been distinguished from CD in terms of immune response, biomarkers, and manifestations (Samaroo et al., 2010). Having antibodies to gliadin and associated GS may represent a subgroup of people with schizophrenia who have a different etiology or manifestation of schizophrenia related to this immune and inflammatory state. The purpose of this study was to replicate the finding of higher AGA antibodies (indicative of gluten sensitivity) in persons with schizophrenia versus a comparison group without schizophrenia. A second purpose was to examine whether symptom profiles in schizophrenia were related to the prevalence of AGA antibodies.

2. Methods

One hundred inpatients or outpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were studied. Participants were between the ages of 18 and 75 years and able to provide informed consent. Patients were not included in this study if they were currently known to have Celiac Disease, Gluten Sensitivity or on a Gluten Free Diet. All participants completed a medical history and were tested for AGA–IgG, AGA–IgA, tTG–IgA, and Endomysial Antibodies (EMA, only if positive for tTG–IgA). Participants also completed a battery of tests including demographic information, the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) and the Calgary Depression Rating Scale (CDS) (Addington et al., 1993). Raters for the BPRS were trained and reliable with Intraclass Correlation Coefficients (ICC) of >0.8 compared to a consensus of experienced raters on total symptom and positive symptom scores. All participants were recruited for this study to examine antibody levels, symptoms and zonulin levels. Zonulin levels have not yet been reported due to assay sensitivity problems to date. No data from this population has not been previously reported on. The population of schizophrenia patients was recruited from the greater Baltimore area through affiliated clinics at the Maryland Psychiatric Research Center.

Assays were performed at the University of Maryland, Center for Celiac Research. The AGA–IgG and IgA, tTG–IgA assays were run on a single ImmunoCap 100 analyzer; Phadia GmbH, Freiburg, Germany. Utilizing an automated enzyme-linked immunosorbent assay (ELISA) method and cuts offs recommended by the manufacturer. The cutoff for a moderate to significant positive for the AGA–IgG and IgA, tTG–IgA assays was ≥7.0. EMA–IgA was detected by indirect immunofluorescence, using monkey esophagus as the substrate; Scimedx Corporation, New Jersey, USA. Fluorescence at a 1:10 dilution or above was considered positive. All samples (cases and controls) were run in batches. Cases were run as they arrived and the controls were done in sequential order of their ID number.

The Center for Celiac Research provided 100 sex and aged (+/−5 years) matched controls for comparison (matching was also attempted for race, but with limited success). Each individual control was screened to insure that they did not have any neurological diagnoses, as reported in their original questionnaire. This population of healthy controls was selected from archived samples from subjects recruited for other studies conducted at the Center for Celiac Research. Informed consent was obtained on all subjects and subjects were located all over the United States.

The mean BPRS total scores and positive symptoms, negative symptoms, hostility, activation and anxiety/depression symptom subfactors (Overall and Gorham, 1988) were compared between the positive and negative antibody groups. Student's t-tests and chi-square tests were used to examine differences between symptoms and antibody levels. These comparisons were made between the healthy controls and the schizophrenia group (combined schizoaffective disorder and schizophrenia diagnoses as the BPRS scores and antibody titers did not differ). The protocol was approved by the University of Maryland Institutional Review Board and all schizophrenia subjects signed informed consent prior to study participation.

3. Results

This study was completed by 100 participants with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and compared to 100 sex and aged matched controls for the prevalence of elevated antibodies. The demographic information of the total samples broken down for schizophrenia and schizoaffective disorder are listed in Table 1. Males comprised 68% and 73% in the schizophrenia and non-schizophrenia control groups, respectively. However, there were significantly fewer males in the schizoaffective disorder group (36%, $p < 0.02$). The mean ages were lower in the schizophrenia groups 32.5 ± 9.9 vs. 40.7 ± 13.1 in the control groups ($t = 4.96$, $df = 184$, $p < 0.0001$). Fifty-eight percent in the schizophrenia samples (57% schizophrenia and 64% schizoaffective disorder) were white as were 89% in the healthy control group (chi-square = 22.35, $df = 1$, $p < 0.0001$).

Ten participants from the schizophrenia group were positive for one or more of the measured antibodies with AGA–IgG being the positive antibody for most (9% positive for gluten sensitivity (AGA) and 1% positive for celiac disease (tTG)). Only one of the 100 matched healthy controls was positive for AGA–IgG and none for tTG; the difference in GS between the two samples was statistically significant (chi-square = 6.74, $df = 1$, $p = 0.0094$). The specific demographic information for the participants with positive antibodies is listed in Table 2. In addition, mean AGA–IgG antibody levels were significantly higher in the schizophrenia groups than the healthy controls. Mean antibody levels did not differ in the AGA–IgA or tTG groups (See Table 3).

Participants in the schizophrenia groups who were AGA-positive ($N = 9$) were slightly younger with an average age of 26.50 ± 5.8 years compared to 33.2 ± 10.0 years in the AGA-negative schizophrenia group ($t = 1.96$, $df = 97$, $p = 0.0526$). The AGA-positive and negative groups did not differ on race and sex. Twenty-two percent (2/9) of those who were positive for AGA were Asian while 1 of 90 were Asian in the AGA-negative group (Fisher's

exact test, p = 0.021). This is a very small difference but worthwhile to point out for future hypotheses.

To examine clinical symptom differences within the schizophrenia group, psychiatric symptoms including positive, negative and depressive symptoms were compared between the AGA-positive and AGA-negative participants. There were no significant differences in RBANS scores for neurocognitive function or in symptom scores on the BPRS or the Calgary Depression Score (Table 2). The only difference was a small reduction in the three item BPRS positive symptom score (sum of items for hallucinations, delusions and conceptual disorganization) in the AGA-positive group (4.11 ± 1.36 vs. 6.39 ± 2.99; t = 5.38, df = 1. p = 0.020) (Table 4).

4. Discussion

This study confirms the increased prevalence of gluten sensitivity and higher AGA–IgG levels in persons with schizophrenia and schizoaffective disorder as compared to the general population. The results show that less severe positive symptoms are more prevalent in AGA-positive schizophrenia patients. This finding differs from a much larger prior study which did not find such a difference (Cascella et al., 2011). It is possible that site to site heterogeneity of clinical ratings may have been present. The current study has the benefit of standardized rater training in a small group of raters with ongoing reliability testing. Despite this, the only finding is that positive symptoms are significantly lower. The small sample size of the AGA-positive group may limit the ability to completely evaluate this association and further studies to examine this relationship may be appropriate. This finding is similar to a recent study in a German sample using the Positive and Negative Symptom Scale (PANSS) linked elevated AGA titers, which revealed significantly lower total symptom levels (PANSS scores and general psychopathology scores), however, they reported no differences in positive and negative symptoms (Okusaga et al., 2013).

While significantly higher rates of AGA positive patients were seen in this study compared to healthy controls, the rates are lower than we reported previously (Cascella et al, 2011). In this study we were using a different antibody assay than we previously reported. This is an important point to note that many different tests are available, some with and without FDA approval and this likely explains the lower prevalence of AGA positive schizophrenia cases as we and others have reported before. We are currently using an FDA approved first generation test by INOVA for all future studies and also the test used by our original CATIE study. Clinicians and researchers need to know that different tests may give different results and standardization in the field is needed in this area. Our group is working on a study to examine the differences of the sensitivity of INOVA first and second generation testing kits.

It is now widely known that approximately 10–25% of people with schizophrenia will test positive for AGA and be considered gluten sensitive. Despite the small sample size, our results suggest that a symptom profile will not distinguish people with schizophrenia and GS from people with schizophrenia who do not have GS. Therefore, a blood test is the only way to determine which people are GS. This is of critical importance as this AGA-positive group with schizophrenia may benefit from the removal of gluten from the diet. A recent pilot

study of two subjects who were AGA-positive showed that the removal of gluten may have rapid and robust effects on positive and negative symptoms of the illness (Jackson et al., 2012a); (Feldman et al., 2013). While the exact relationship is not yet understood, a number of mechanisms have been proposed in light of the many associations between gluten and schizophrenia and the immune pathway is leading with regard to understanding how antibodies to gluten may play a role in symptoms. This strategy may provide an innovative biomarker to identify an appropriate and effective treatment for a specific subsample of people with schizophrenia.

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Table 1

Demographic information of the groups.

	DSM-IV diagnosis N = 100		Healthy control N = 100	Statistics
	Schizophrenia N = 86[a]	Schizoaffective disorder N = 14		
Age	31.5 (9.4)	38.7 (10.7)	40.7 (13.1)	F = 14.9, df = 2, p < 0.0001
Male	63 (73.3%)	5 (35.7%)	67 (67.7%)	Chi-square = 7.8, df = 2, p = 0.0204
White	49 (57.0%)	9 (64.3%)	79 (88.8%)	Chi-square = 22.7, df = 2, p < 0.0001
BPRS	31.5 (6.7)	33.6 (6.4)		T = 1.49, df = 1, p = 0.2227
BPRS total score	6.1 (3.0)	6.9 (2.9)		T = 1.28, df = 1, p = 0.2587
BPRS positive symptoms	5.8 (2.4)	6.5 (2.2)		T = 1.48, df = 1, p = 0.2243
BPRS anxiety/depression	4.4 (1.7)	4.9 (1.7)		T = 1.27, df = 1, p = 0.2590
BPRS hostility	6.7 (2.6)	6.8 (2.6)		T = 0.01, df = 1, p = 0.9162
BPRS negative symptoms	4.0 (1.4)	3.7 (1.4)		T = 1.49, df = 1, p = 0.2222
BPRS activation?				
RBANS total score	73.1 (16.0)	76.8 (20.2)		T = 0.04, df = 1, p = 0.8383
Calgary Depression Score	76.6 (19.8)	84.2 (24.5)		T = 0.04, df = 1, p = 0.8383

[a] One person was considered psychotic disorder NOS and included in the schizophrenia group.

Table 2

Demographics for antibody-positive subjects.

	Positive antibody	Schizophrenia subtype	Gender	Race	Age
Participant 1	AGA–IgG	Undifferentiated	M	Caucasian	49
Participant 2	AGA–IgG	Paranoid	M	Black	46
Participant 3	AGA–IgG	Paranoid	M	Caucasian	24
Participant 4	AGA–IgG	Schizoaffective, depressive type	F	Black	23
Participant 5	AGA–IgG+ AGA–IgA	Schizoaffective, manic type	F	Black	28
Participant 6	AGA–IgG	Paranoid	M	Black	30
Participant 7	AGA–IgA	No data	F	Asian	39
Participant 8	AGA–IgG	Residual	M	Asian	29
Participant 9	AGA–IgG	Undifferentiated	M	Caucasian	25
Participant 10[a]	EMA+ tTG–IgA	Paranoid	F	Caucasian	45
Control 1	AGA–IgG	Healthy control	M	Caucasian	24

[a]This participant was positive for celiac disease assays and not gluten sensitivity. This person was not included in the gluten sensitive schizophrenia group (N = 9).

Table 3

Mean antibody levels by group.

	Schizophrenia N = 100	Healthy controls N = 100	Statistics
AGA–IgG	2.9 (7.7)	1.3 (1.3)	T = −2.01, df = 104.3, p = 0.0475[a]
AGA–IgA	2.0 (1.5)	1.9 (0.9)	T = −0.87, df = 162.6, p = 0.3861
tTG–IgA	0.8 (0.9)	1.0 (0.7)	T = 1.03, df = 198, p = 0.1547

[a]Statistics after controlling for age (F = 4.02, df = 1, p = 0.0464).

Table 4

Symptoms scores in antibody-positive and negative schizophrenia subjects.

	AGA positive (mean ± SD) N = 9	AGA negative (mean ± SD) N = 90[a]	T	Df	p value
Calgary Depression Rating Scale	1.22 ± 1.48	1.84 ± 2.23	0.58	1	0.447
BPRS total score	28.56 ± 3.09	32.15 ± 6.84	2.40	1	0.121
BPRS positive symptoms	4.11 ± 1.36	6.39 ± 2.99	5.38	1	0.020
BPRS negative symptoms	6.56 ± 2.51	6.71 ± 2.61	0.01	1	0.922
BPRS hostility	4.11 ± 1.17	4.52 ± 1.75	0.20	1	0.651
BPRS anxiety/depression	5.33 ± 1.80	6.00 ± 2.47	0.46	1	0.499
BPRS agitation	4.11 ± 1.27	3.94 ± 1.38	0.30	1	0.586
RBANS total score	71.89 ± 17.30	73.62 ± 16.60	0.10	1	0.755
Acid Relux/GERD[b]	1 (11%)	11 (12%)			
Constipation	0	4 (4%)			
Types I or II diabetes	1 (11%)	16 (18%)			

[a] Excludes the tTG- and EMA-positive, but AGA negative participant.

[b] Gastrointestinal reflux/GERD (gastroesophageal reflux disease) and constipation were the only gastrointestinal symptoms noted on the medical examination. One person had Crohn's disease in the AGA negative schizophrenia group.