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Prevalence of Celiac Disease and Gluten Sensitivity in the United States Clinical Antipsychotic Trials of Intervention Effectiveness Study Population

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Celiac disease (CD) and schizophrenia have approximately the same prevalence, but epidemiologic data show higher prevalence of CD among schizophrenia patients. The reason for this higher co-occurrence is not known, but the clinical knowledge about the presence of immunologic markers for CD or gluten intolerance in schizophrenia patients may have implications for treatment. Our goal was to evaluate antibody prevalence to gliadin (AGA), transglutaminase (tTG), and endomysium (EMA) in a group of individuals with schizophrenia and a comparison group. AGA, tTG, and EMA antibodies were assayed in 1401 schizophrenia patients who were part of the Clinical Antipsychotic Trials of Intervention Effectiveness study and 900 controls. Psychopathology in schizophrenia patients was assessed using the Positive and Negative Symptoms Scale (PANSS). Logistic regression was used to assess the difference in the frequency of AGA, immunoglobulin A (IgA), and tTG antibodies, adjusting for age, sex, and race. Linear regression was used to predict PANSS scores from AGA and tTG antibodies adjusting for age, gender, and race. Among schizophrenia patients, 23.1% had moderate to high levels of IgA-AGA compared with 3.1% of the comparison group ($\chi^2 = 1885$, $df = 2$, $P < .001$.) Moderate to high levels of tTG antibodies were present in 5.4% of schizophrenia patients vs 0.80% of the comparison group ($\chi^2 = 392.0$, $df = 2$, $P < .001$). Adjustments for sex, age, and race had trivial effects on the differences. Regression analyses failed to predict PANSS scores from AGA and tTG antibodies. Persons with schizophrenia have higher than expected titers of antibodies related to CD and gluten sensitivity.

Key words: anti-gliadin IgA antibodies/tTG antibodies/EMA antibodies/PANSS

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains including wheat, rye, and barley in genetically susceptible individuals.[1] The disease can manifest itself with a range of clinical presentations including the typical malabsorption syndrome and a spectrum of symptoms affecting any organ including the peripheral and central nervous system. A wide range of neurologic conditions including cerebellar ataxia,[2] cerebral atrophy and dementia,[3] cerebral vasculitis,[4] brain stem encephalitis,[5] and an increased risk of epilepsy[6] have all been previously described in association with CD. Likewise, psychiatric conditions including anxiety and depression,[7,8] attention deficit/hyperactivity disorder,[9] eating disorders,[10] and autism[11] have been also associated with CD. Because CD often presents in an atypical or even silent manner, many cases remain undiagnosed.

CD affects between 0.3%–1% of the European population[12] and a lower percentage of Africans,[13] Asians,[14] and South Americans.[15] In the United States, the overall prevalence has been estimated to be around 0.75%.[16] Given that the prevalence of schizophrenia is between 0.5% and 1% of the population, a high number of comorbid cases of the 2 conditions would be unexpected. Recent epidemiologic data further highlighting the association between schizophrenia and several autoimmune diseases including celiac[17] have showed a higher prevalence of CD among patients with schizophrenia than matched comparison subjects in a Danish sample. Using data from about 7000 people admitted to a Danish psychiatric facility for the first time between 1981 and 1998, the adjusted relative risk for onset of schizophrenia for people with a history of CD was 3.2 (95% confidence interval [CI] = 1.8–5.9), while no association was found with 2 other autoimmune intestinal diseases, Crohn

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and ulcerative colitis.[18] The association is strong but reflects a small proportion of cases of either disorder because both clinical conditions are rare. Although the reasons for this higher co-occurrence are not known and several hypotheses have been advanced,[19] the clinical knowledge about the presence of immunologic markers for CD or gluten sensitivity in patients with schizophrenia may have profound implications for the treatment of these subjects given that gluten-free diet can potentially contribute to the improvement of their symptoms.[20]

The present study obtained samples of blood from 1401 patients with schizophrenia who had participated in the Clinical Antipsychotic Trials of Intervention Effectiveness or CATIE[21] and assessed the prevalence of antibodies to gliadin (AGA), transglutaminase (tTG), and endomysium (EMA).

Methods

Study Participants

Individuals were eligible for participation in the CATIE study if they were aged 18–65 years, had received a *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder currently or in the past, and were judged appropriate for treatment with oral antipsychotic medications. The CATIE study, sponsored by the National Institute of Mental Health, wanted to address the issue of the relative effectiveness of second-generation (atypical) antipsychotic drugs as compared with that of older agents. Patients with schizophrenia were recruited at 57 US sites and randomly assigned to receive olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months (see Lieberman et al,[21] for more detailed information about study methods). Serum was available for 1401 participants (1323 with a diagnosis of chronic schizophrenia, 76 with a diagnosis of schizoaffective disorder, and 2 with schizophreniform disorder) of the 1460 who participated in phase I of the CATIE trial, and this served as the sample for the schizophrenia cases examined. The comparison group ($N = 900$) was composed of attendees at primary health-care units who answered a questionnaire indicating elevated risk for CD in a study by Catassi et al.[22] This comparison group thus has some degree of selection for positive assays. There was no screening of the comparison group for schizophrenia, so the best estimate would be that less than 1% of that group meets criteria for schizophrenia. Consumption of wheat-containing products is assumed to be equivalent in the CATIE group and control groups based on the United States Department of Agriculture's data on wheat consumption in the United States (www.ers.usda.gov).

Measurements

All blood samples, from the CATIE study and comparison group, were screened at the University of Maryland Center for Celiac Research using the human tissue transglutaminase (hTTG) immunoglobulin (Ig) A enzyme-linked immunosorbent assay (ELISA) as we have previously described.[23] Kits from INOVA Diagnostics, Inc (San Diego, CA) were used for the assessment of the CATIE sample. The comparison group, collected between 2002 and 2004, was assayed using Scimedx (Denville, NJ) kits provided by the company for that study.[22] Both kits use equivalent methods for antibody detection. All hTTG-positive samples were also tested for the presence of IgA EMA by applying an immunofluorescence method using human umbilical cord vein or monkey esophagus as substrate.[24] A positive fluorescence at dilutions equal to or greater than 1:10 was considered positive.

Presence of AGA-IgA and -IgG was measured by ELISA also using the INOVA kit and using cutoffs as recommended by the manufacturer. Serum samples testing positive for AGA-IgG but not AGA-IgA were tested for total IgA concentration to detect IgA deficiency. CD is here defined by a combination of EMA-positive and/or tTG-IgA–, and AGA-IgA–positive antibodies. Psychopathology of the study's participants was assessed using the Positive and Negative Symptoms Scale or PANSS.[25]

Statistical Analysis

The χ^2 test for comparison of populations was applied to assess for statistical difference in the frequency of AGA-IgA and tTG antibodies in the CATIE population compared with the comparison samples. Logistic regression was used to adjust for possible group differences in age, race, and sex that might confound the observed relationship. Linear regression analyses using STATA 10 were conducted to predict baseline PANSS total scale scores from AGA and tTG serum antibodies, adjusting for age, gender, and race. Statistical analysis included separate testing for IgA-tTG and AGA serum antibodies using both 2-level measures (any increase vs none) and 3-level measures (moderate and severe vs none). PANSS outcome was analyzed for total PANSS score and scores for PANSS subscales. All tests were 2 tailed, and significance was defined as an $\alpha < .05$. One-tailed tests were conducted for total PANSS above the most frequently used clinical cutoff point (>95).[26]

Results

In this study, the schizophrenia group consisted of 1401 serum samples, and 900 serum samples were available for the comparison group. The schizophrenia group from the CATIE sample had a mean age of 40.6 ± 11.1 years. The gender distribution consisted of 74% males and 26% females. The distribution by race was made by 60% Caucasians, 35% African Americans, and 5% other races. The

Table 1. Assays on Subjects From CATIE Trials and Comparison Samples

	tTG Antibodies		IgA-Antigliadin Antibodies	
	CATIE (N = 1401)	Comparison, (N = 900)	CATIE, (N = 1401)	Comparison, (N = 900)
Total positive[a] (medium plus high)	76 (5.4%)	7 (0.80%)	323 (23.1%)	28 (3.1%)
Low	1325 (94.6%)	893 (99.2%)	1078 (76.9%)	872 (96.9%)
Medium	55 (3.9%)[b]	7 (0.80%)[b]	155 (11.1%)[c]	16 (1.8%)[c]
High	21 (1.5%)[b]	0[d]	168 (12.0%)[c]	12 (1.3%)[c]
	100.0%	100.0%	100.0%	100.0%

Note: Standard statistical rounding was used across test results. CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; tTG, antibody to transglutaminase; IgA, immunoglobulin A.
[a]The cutoff scores are expressed as arbitrary units established by the manufacturers. INOVA Diagnostics, Inc—cutoff scores for tTG-antibody to gliadin (AGA) and AGA-IgA are each set at the same level: low or negative, <20 units; weak positive, 20–30 units; strong positive >30 units. Scimedx—cutoff scores are negative, <7; positive, >7. INOVA Diagnostics, Inc, kits were employed for CATIE sample tTG tests and all AGA tests. Scimedx kits were employed for comparison tTG tests.
[b]$\chi^2 = 392.0$, $df = 2$, $P < .001$.
[c]$\chi^2 = 1884.6$, $df = 2$, $P < .001$.
[d]The manufacturer does not distinguish medium from high; therefore, subjects above the threshold for "low" were placed in the medium category to be conservative.

comparison group had a mean age of 53 ± 18.3 years, consisted of 25% males and 75% females, and included 808 Caucasians (90%), 48 African Americans (5.3%), and 44 other races (4.7%). CATIE and comparison subjects differed at a statistically significant level by age ($t = 20.2249$, $df = 2299$, $P < .001$), gender ($\chi^2 = 1811.107$, $df = 1$, $P < .001$), and race ($\chi^2 = 2444.025$, $df = 4$, $P < .001$).

The schizophrenia group from the CATIE sample had significantly higher prevalence of antibodies to tTG and AGA than the comparison samples (table 1). Of the CATIE sample, 23.1% had moderate to high levels of AGA-IgA compared with only 3.1% of the comparison group (relative odds of 9.4; $\chi^2 = 1885$, $df = 2$, $P < .001$). In total, 5.4% of the CATIE schizophrenia population and 0.80% of the comparison group had moderate to high levels of tTG antibodies (relative odds of 7.1, $\chi^2 = 392$, $df = 2$, $P < .001$). There were 5 (0.35%) CATIE subjects positive on the EMA assay. A low number of patients, 1.4% of the CATIE sample, had positive AGA-IgG in contrast to 3.3% of normal controls with positive AGA-IgG. None of the demographic factors, age, gender, and race, was significantly different for the 3-level distribution of tTG-IgA (see Table 3). Schizophrenia patients who were AGA-IgA positive were significantly different by race but not by age or gender (see Table 3). Because CATIE and comparison subjects differed at a statistically significant level by age, gender, and sex, we used a logistic regression analysis to assess if differences on tTG-IgA and AGA-IgA were still significant after accounting for the effect of age, gender, and sex. For tTG, the significance of group differences was not changed after adding gender (odds ratio [OR] = 9.1, $P < .0001$, 95% CI = 4.0–20.5), age (OR = 6.0, $P < .0001$, 95% CI = 2.6–13.6), and race (OR = 6.6, $P < .0001$, 95% CI = 3.0–14.6) or all 3 (OR = 6.6, $P < .0001$, 95% CI = 2.8–15.6).The same was true for AGA-IgA after adding gender (OR = 10.0, $P < .0001$, 95% CI = 6.6–15.2), age (OR = 10.1, $P < .0001$, 95% CI = 6.5–15.7), and race (OR = 8.1, $P < .0001$, 95% CI = 5.4–12.1) or all 3 (OR = 9.2, $P < .0001$, 95% CI = 5.8–14.8).

In the schizophrenia group from the CATIE cohort, the mean baseline PANSS total score was 73.5 (SE = 1.91, 95% CI = 69.7–77.2) for those with tTG-positive antibodies ($N = 76$) compared with 75.8 (SE = 0.48, 95% CI = 74.8–76.7) for those who were tTG negative ($N = 1315$) ($t = 1.1228$, $df = 1389$, $P < .26$). Also, the mean PANSS total scores were 76.5 (SE = 0.96, 95% CI = 74.7–78.4) and 75.4 (SE = 0.54, 95% CI = 74.3–76.4) for those who were ($N = 322$) and were not ($N = 1069$) positive for IgA-AGA antibodies, respectively ($t = 1.0449$, $df = 1389$, $P < .029$). These differences are neither statistically nor clinically significant.

The tTG or AGA antibodies were not related to clinical characteristics as measured by the baseline total score on the PANSS scales. Table 2 shows the linear regressions conducted to predict baseline PANSS total score and subscores from AGA and tTG serum antibodies, adjusting for age, gender, and race. Measures of AGA-IgA as a dichotomous measure (>20 vs <20) revealed no differences and failed to produce significant results (not shown). Likewise, tTG-IgA measurements also did not reach a level of statistical significance in predicting PANSS scores. Additional analysis (not shown) compared symptoms of schizophrenia for the markedly or severely ill (PANSS total score >95) with those moderately ill or less (<95).[26] None of the serum measures were associated with baseline PANSS scores at an important or statistically significant level.

Table 2. Association of Assays With PANSS Scale Scores in 1391 CATIE Subjects

	PANSS Scale Score[a]					
	Positive		Negative		Total	
	b	SE	*b*	SE	*b*	SE
Model 1						
Age (mean)	−0.01	0.01	−0.03	**0.02**	−0.09	**0.04**
Female (vs male)	−0.50	0.35	−0.90	**0.40**	−0.86	1.09
African American (vs Caucasian)	0.01	0.32	0.28	0.36	−1.23	1.00
Other (vs Caucasian)	0.52	0.72	1.51	0.81	2.98	2.23
Medium tTG (vs low)[b]	0.92	0.78	−1.45	0.88	−1.97	2.42
High tTG (vs low)	−0.51	1.24	1.25	1.40	−1.45	3.85
Model 2						
Age (mean)	−0.01	0.01	−0.03	**0.02**	−0.10	**0.04**
Female (vs male)	−0.53	0.35	−0.91	**0.40**	−0.95	1.09
African American (vs Caucasian)	−0.04	0.32	0.24	0.37	−1.39	1.01
Other (vs Caucasian)	0.51	0.72	1.44	0.81	2.82	2.23
Medium AGA (vs low)	0.75	0.49	0.42	0.55	1.93	1.51
High AGA (vs low)	0.45	0.47	0.40	0.53	1.09	1.46

Note: PANSS, Positive and Negative Symptoms Scale; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; tTG, antibody to transglutaminase; AGA, antibody to gliadin.
[a]Parameters are bold face when significant at $P < .05$; none were significant at $P < .01$.
[b]Adjusted for sex, age, and race.

Discussion

Reaction to gluten can involve either an allergic reaction (wheat allergy) or a nonallergic response (gluten sensitivity) or an autoimmune response in subjects genetically predisposed (CD). The most important finding of this study is the elevated proportion of schizophrenia patients, compared with a comparison sample of individuals not selected for schizophrenia, with moderate to high titer of AGA of the IgA type indicating the existence of a specific immune response to gluten in this population. One out of 4.3 people with schizophrenia was positive for IgA-AGA as compared with only one out of 32.1 in the control population.

A preliminary study,[27] based on a small number of patients and controls ($N = 13$), reported a "median" increase in specific IgA-AGA in patients with a *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) (*DSM-III-R*) diagnosis of schizophrenia. Interestingly, the increase in IgA-AGA was the same in a control group of patients free of neuroleptic treatment for 3 months indicating that the IgA elevation was independent from medications. No difference in IgA-AGA level was observed when the patients were divided into clinical subtypes. The study's relevance is limited by the small sample size and the lack of comparison prevalence data. Another study[28] found decreased levels of IgA and IgG in response to cell constituents like actin, tubulin, and myosin in the serum of *DSM-III-R* patients with schizophrenia, but AGA was not measured. This last finding seems to suggest a lesser damage to cells in patients with schizophrenia compared with normal controls.

If we consider the serologic test combination representing CD (ie, EMA and/or tTG plus AGA-IgA), the calculated prevalence ($N = 29$) in the CATIE schizophrenia sample is 2.1%, more than double of the general population estimate. Previous estimates of CD in schizophrenia have indicated a proportion of 2.6%.[19] Because most studies examining CD in schizophrenia, published to date, did not use optimally sensitive detection methods, like the assay for tTG antibodies developed in the late 90s,[23] they are likely to have underestimated the true proportion positive. A recent study reported results solely on the presence of anti-EMA and not other markers for CD or gluten sensitivity. This study showed no positive cases in the 50 subjects sampled.[29] The same was found in a population-based study that showed no association between CD and a diagnosis of schizophrenia.[30] A recent Scandinavian report[31] showed an association of CD diagnosed according to *International Classification of Diseases, Eighth, Ninth, and Tenth Revisions*, criteria and risk of nonaffective psychosis but not schizophrenia.

These findings are consistent with our results from the CATIE sample that has showed a moderately increased prevalence of tTG antibodies, a dramatically increased prevalence of AGA-IgA, and a low prevalence of anti-EMA. A possible explanation for this discrepancy is that, while both assays detect antibodies against the same autoantigen (transglutaminase), the tTG assay is an ELISA test (more sensitive) compared with the

Table 3. Characteristics of Positive Assays in 1401 CATIE Subjects

	Serum Levels		Sample Total	% Positive
	Weak Positive tTG = >20 and <30	Strong Positive tTG ≥ 30		
Age at interview				
Mean years	45.1	43.6	40.6	
SE	1.147	1.873	0.296	
Gender				
Males	38	13	1040	4.9
Females	17	8	361	6.9
Total			1401	
Race/ethnicity[a]				
White	29	11	843	4.7
Black	22	9	488	6.3
Other[b]	4	1	68	7.4
Total			1399	
	AGA = >20 and <30	AGA ≥ 30	Sample Total	% Positive
Age at interview				
Mean years	41.1	42.4	40.3	
SE	0.835	0.798	0.343	
Gender				
Males	103	126	1040	22.0
Females	52	42	361	26.0
Total			1401	
Race/ethnicity[a]				
White	83	83	843	19.7
Black	63	77	488	28.7
Other[b]	9	8	68	25.0
Total			1399	

Note: CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; tTG, antibody to transglutaminase; AGA, antibody to gliadin.
[a]Race data are missing on 2 subjects.
[b]"Other" races for tTG positives were Asians at both the weak and strong serum-positive levels.
[c]"Other" races for AGA positives included weak positive serum level = 1 American Indian or Alaskan Native, 4 Asians, and 4 subjects designated as 2 or more races; strong positive serum level = 1 American Indian or Alaskan native, 2 Asians, 2 native Hawaiian of other Pacific islander and 3 subjects designated as 2 or more races.

operator-dependent anti-EMA antibody test (immunofluorescence assay). It is also possible that patients with schizophrenia suffer from mild intestinal tissue damage, as subjects with milder intestinal tissue damage are thought to test positive for tTG and negative with EMA. Another explanation could be related to the existence of an extraintestinal source of tTG in the CATIE population given that the discrepancy between the 2 tests is usually detected in specific autoimmune diseases, such as type 1 diabetes, autoimmune hepatitis, and autoimmune thyroid conditions.[32] We believe that the most likely explanation is that patients with schizophrenia suffer from mild intestinal tissue damage that might also be consistent with the extremely low number of EMA-positive cases found in this study. A recent study[33] has showed that subjects with gluten sensitivity have normal intestinal permeability and normal expression of tight junction proteins suggesting a different pathogenic mechanism from CD.

The serologic characterization of our sample appears to identify 2 groups of patients. The major group is represented by patients with elevated AGA-IgA identifiable as having gluten sensitivity and the second group with a smaller but still unusually high proportion with a combination of antibodies more characteristic of CD (ie, EMA and/or tTG plus AGA-IgA). Although it is unknown why there is a preferential immunologic response with IgA to gluten constituents by patients with schizophrenia while normal controls respond with both IgA and IgG in almost equal percentages (3.3% IgG and 3.1% IgA in controls vs 1.4% IgG and 23.1% IgA in CATIE patients), we can hypothesize that a subgroup of patients with schizophrenia might have a genetically regulated mechanism that favors the switch of immunoglobulin response toward

IgA. Alternatively, this subgroup of patients might have an increased concentration of transforming growth factor β (TGF-β) that usually regulates the switch toward the production of IgA,[34] or altered levels of cytokines like interleukin (IL)-13 that stimulate the production of TGF-β[35] might be invoked to explain our findings.

An association between CD and schizophrenia was noted in reports spanning back to the 1950s.[36,37] An interpretation of these early findings was that gluten may serve as an environmental trigger for schizophrenia in genetically susceptible individuals and that patients with schizophrenia share one or more genes with CD.[38] The majority of individuals with CD possess HLA-DQ2 (DQA1*05/DQB1802 haplotype) and the remainder HLADQ8 (DQA1*0301/DQB1*0302 haplotype).[39] Schizophrenia has also been associated with HLA-DQB1[40] though the results have been more controversial compared with CD and the initial findings not always replicated[41,42] raising the possibility of a lack of association with this HLA locus or that the well-known heterogeneity of schizophrenia may have confounded the results. Genetic linkage studies for non-HLA loci for CD and for schizophrenia suggest otherwise several areas of overlap. A genetic marker, 6p23-p22.3, implicated in CD in a study in western Ireland[43] is adjacent to the dysbindin locus (6p22.3), which has been implicated in schizophrenia in an independent study of the same population.[44] Recent studies have also shown susceptibility regions for CD in chromosome 11q23[45] that overlaps with a potential schizophrenia susceptibility region.[46] A more recent study has suggested MY09B marker for both diseases on chromosome 19 though the value of this finding is difficult to interpret given that variants were located at the intron and not the exon of the gene.[47] A genome-wide association study for CD has identified risk variants in the region harboring cytokines IL-2 and IL-21[48] indicating a potential overlap with reported abnormal cytokines functioning in schizophrenia including IL-2.[49]

Schizophrenia is conceptualized by many as a heterogeneous disorder. A growing literature suggests that immune mechanisms are responsible for schizophrenia or some proportion of it. The literature includes epidemiologic data showing that a history of autoimmune disease in the subject, or in the parent, prior to onset, raises risk for schizophrenia by 45%.[17] Limitations of this study include its retrospective nature and the use of a historical control group not drawn from the same area or at the same time of the CATIE population. As already stated, wheat consumption in the United States is thought to be evenly distributed, so it is unlikely that the CATIE sample wheat consumption was different from that of the control group such that our findings would be explained by exposure to different environmental factors. A second limitation is the lack of confirmatory biopsy in those case subjects who met criteria for CD based on serum tests. Another limitation is the use of different diagnostic kits for tTG analysis though the data cannot be explained on the basis of the different kits used given that both use equivalent methods for antibody detection.

There are numerous comparisons of immunologic parameters of persons with schizophrenia to healthy persons, with results of varying consistency across different studies. Our results confirm the existence of a subgroup of patients with antibody characteristics associated with the presence of a specific immune response to gluten. We have failed to identify clinical aspects associated with such immune response. Nonetheless, the findings may have potential implications for the treatment of these subjects given that a gluten-free diet can contribute to the improvement of their symptoms.

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