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A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies

Jessica Jackson,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

William Eaton,
Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205, USA

Nicola Cascella,
Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205, USA

Alessio Fasano,
University of Maryland Baltimore School of Medicine, Mucosal Biology Laboratory and the Center for Celiac Research, 655 West Baltimore Street, Baltimore, MD 21201, USA

Dale Warfel,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Stephanie Feldman,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Charles Richardson,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Gopal Vyas,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Jared Linthicum,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Debby Santora,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Kimberly R. Warren,
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA, Morgan State University, 1700 East Cold Spring Lane, Baltimore, MD 21251, USA

William T. Carpenter, and

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*Corresponding author at: Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA. Tel.: +1 410 402 6861; fax: +1 410 402 6880. dkelly@mprc.umaryland.edu.

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University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA, VA Capitol Health Care Network (VISN 5) MIRECC, 209 West Fayette Street, Baltimore, MD 21201, USA

Deanna L. Kelly
University of Maryland Baltimore School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA

Dear Editors

Celiac disease is an immune-mediated disease involving a reaction to gluten, presenting with diarrhea, weight loss, abdominal complaints and a range of less common associated neurologic and psychiatric symptoms. Several epidemiologic studies have linked celiac disease to schizophrenia, however only recently have direct antibody assessment for the detection of celiac disease (anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies (EMA)) become available (reviewed in Kalaydjian et al., 2006). Antibodies to gliadin (AGA) and not anti-tTG suggest an immune-mediated reaction distinct from celiac disease, gluten sensitivity. Gluten sensitivity is thought to be associated with neurologic and psychiatric manifestations, but free from the gastrointestinal symptoms seen in celiac disease (Jackson et al., 2012), however this separation has only recently been recognized. In a previous study by our group, we identified the prevalence of gluten-related antibodies in people with schizophrenia. Using blood samples from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) we found that 5.5% of the sample with schizophrenia had a high level of anti-tTG antibodies (compared to 1.1% of the healthy control sample). This group also showed a rate of 23.1% (age-adjusted) having AGA (compared to 3.1% of the comparison sample) (Cascella et al., 2011), but not having anti-tTG antibodies. Other estimates confirming the higher prevalence of antibodies to anti-tTG and AGA among people with schizophrenia have also been published (Dickerson et al., 2010; Jin et al., 2012). Seven clinical trials have been conducted to test the assertion that a gluten-free diet (GFD) may improve remission of schizophrenia symptomatology. These early studies had mixed results because they included schizophrenia patients not tested for antibodies (reviewed in Kalaydjian et al., 2006). However, there are cases of gluten removal and complete resolution of schizophrenia symptoms (Jansson et al., 1984; De Santis et al., 1997; Kraft and Westman, 2009).

This open label pilot study was designed to test the feasibility and efficacy of a GFD in people with schizophrenia positive for either anti-tTG or EMA, suggesting celiac disease, or AGA, indicating gluten sensitivity. Two participants, one positive for anti-tTG and the other AGA, were recruited for a two-week inpatient trial with one-on-one supervision to ensure compliance to the GFD. Participants met DSM-IV criteria for schizophrenia, were clinically stable and on the same antipsychotic medication for two months with an unchanged dose for the 4 weeks prior to starting the trial. One reliable research staff performed ratings for each participant throughout the two-week study. This two-week study was Institutional Review Board approved and all participants passed the Evaluation to Sign Consent prior to signing consent. Table 1 shows the demographic information of the two participants along with their change in symptomatology and side effects.

Our results suggest that a GFD in people with antibodies to anti-tTG or AGA may lead to symptom improvements in schizophrenia as well as robust improvements in extrapyramidal side effects (EPS). Both participants saw notable improvements on the BPRS and SANS. Both participants also had improvements in akathisia and EPS with participant B having notable changes in both at the end of the trial. The data shows that a GFD can be maintained in individuals with schizophrenia with no negative effects on behavior or attitude and no

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need for medication changes. Overall the diet was easily maintained, however it is recognized that much education would be needed to help patients understand the importance of a GFD and the gluten content of food and snacks.

The pilot study is obviously limited by the small sample and no control group or placebo; however no studies to date have been performed in antibody-positive patients and with the robust findings, this information is critical to share with the field to encourage future research in this area. Other potential limitations are the short period of withdrawal from gluten and that the improvements could be in part due to participants entering an experimental treatment protocol in general. A longer-term study may produce more robust changes over time. Bowel symptoms in celiac disease are often rapidly improved when a patient begins a GFD, but there is insufficient data to discern how long it takes to see improvement in gluten sensitivity and in related neurological and behavioral symptoms (A. Fasano, personal communication). Participant B was still positive for AGA–Ig A at the end of the two-week trial suggesting he may need more time on a GFD to see the full extent of improvement. With resolution of antibodies we would hope for continued improvement in symptoms. Adhering to a GFD is not easy but is quite feasible with sufficient motivation, as shown in a recent meta-analysis of 38 studies (Hall et al., 2009). With the pipeline of treatments for schizophrenia lacking novel candidates, this potential mechanism is exciting and may provide improvement for up to one-fourth of patients (antibody-positive) who suffer from this devastating disorder. More research is critically needed to determine a proof of concept study in order to show that removing gluten from the diet is an effective treatment in antibody-positive patients with schizophrenia.

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Table 1

Participant characteristics.

		Clinical notes	BPRS	SANS	CGI	PGI	SF- 36	SAS	BAS	BMI (kg/m^2)	Antibodies[a]
Participant A (female) Antipsychotic meds:olanzapine15 mg bid, aripiprazole 20 mg daily	Baseline	Symptomatic since 1976, disordered thought and positive symptoms	55	48	5	4	118	3	0	23.2	24.0 U/mL[b] Anti-tTG IgA
	Endpoint	Improved concentration and attention	44	39	4	1	122	2	0	23.6	0.9 U/mL Anti-tTG IgA
Participant B (male) Antipsychotic Meds: clozapine 50 mg qam and 350 mg QHS,	Baseline	Symptomatic for 8 years with 4 year prodrome, significant delusions	40	60	4	4	126	3	5	23.1	16.0 U/mL[b] AGA IgG
	Endpoint	Improved insight, free of many psychotic ideas	34	42	4	4	130	0	2	22.5	13.0 U/mL AGA IgG

BPRS — Brief Psychiatric Rating Scale

SANS — Scale for the Assessment of Negative Symptoms

CGI — Clinical Global Impression

PGI — Patient Global Improvement

SF-36 — Short Form 36

SAS — Simpson Angus Scale

BAS — Barnes Akathisia Scale

BMI — body mass index

Anti-tTG — anti-tissue transglutaminase antibodies

AGA — anti-gliadin antibodies

IgA — immunoglobulin A

IgG — immunoglobulin G

Positive>10, Equivocal 7–10, Negative<7. Both participants were tested for IgA tTG, IgA AGA and IgG AGA. Negative values were not recorded.

[a]The samples were run on an instrument and not an ELISA plate. The instrument: Immuno Cap 100 from Phadia.

[b]Baseline antibody values were reported 2 weeks prior to the 2 week clinical trial, thus this change reflects a 4 week time period.