Schizophrenia Research 159 (2014) 539–542

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Gluten sensitivity and relationship to psychiatric symptoms in people with schizophrenia

Jessica Jackson [a], William Eaton [b], Nicola Cascella [c], Alessio Fasano [d,e], Debby Santora [f], Kelli Sullivan [g], Stephanie Feldman [g], Heather Raley [h], Robert P. McMahon [g], William T. Carpenter Jr. [g], Haley Demyanovich [g], Deanna L. Kelly [g,*]

[a] Temple University School of Medicine, 3500 North Broad Street, Philadelphia, PA 19140, USA
[b] Johns Hopkins Bloomberg School of Public Health, 624 North Broadway, Baltimore, MD 21205, USA
[c] Neuropsychiatry Program Sheppard Pratt Hospital, 6501 North Charles Street, Baltimore, MD 21285, USA
[d] Massachusetts General Hospital for Children, 175 Cambridge Street, Boston, MA 02114, USA
[e] Massachusetts General Hospital East, 16th Street, Charlestown, MA 02129, USA
[f] University of Maryland School of Medicine, 660 West Redwood Street, Baltimore, MD 21201, USA
[g] University of Maryland School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, 55 Wade Avenue, Catonsville, MD 21228, USA
[h] National Institute on Drug Abuse, 251 Bayview Blvd., Baltimore, MD 21223, USA

ARTICLE INFO

Article history:
Received 19 May 2014
Received in revised form 9 September 2014
Accepted 11 September 2014
Available online 11 October 2014

Keywords:
Gluten
Celiac disease
Schizophrenia
Gliadin
Gluten sensitivity

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 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.

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.,

* Corresponding author at: Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA. Tel.: +1 410 402 6861; fax: +1 410 402 6880.
E-mail address: dkelly@mprc.umaryland.edu (D.L. Kelly).

http://dx.doi.org/10.1016/j.schres.2014.09.023
0920-9964/

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

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.