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IgG dynamics of dietary antigens point to cerebrospinal fluid barrier or flow dysfunction in first-episode schizophrenia

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ABSTRACT

Schizophrenia is a complex brain disorder that may be accompanied by idiopathic inflammation. Classic central nervous system (CNS) inflammatory disorders such as viral encephalitis or multiple sclerosis can be characterized by incongruent serum and cerebrospinal fluid (CSF) IgG due in part to localized intrathecal synthesis of antibodies. The dietary antigens, wheat gluten and bovine milk casein, can induce a humoral immune response in susceptible individuals with schizophrenia, but the correlation between the food-derived serological and intrathecal IgG response is not known. Here, we measured IgG to wheat gluten and bovine milk casein in matched serum and CSF samples from 105 individuals with first-episode schizophrenia ($n = 75$ antipsychotic-naïve), and 61 controls. We found striking correlations in the levels of IgG response to dietary proteins between serum and CSF of schizophrenia patients, but not controls (schizophrenia, $R^2 = 0.34–0.55$, $p \leqslant 0.0001$; controls $R^2 = 0.05–0.06$, $p > 0.33$). A gauge of blood–CSF barrier permeability and CSF flow rate, the CSF-to-serum albumin ratio, was significantly elevated in cases compared to controls ($p \leqslant 0.001–0.003$). Indicators of intrathecal IgG production, the CSF IgG index and the specific Antibody Index, were not significantly altered in schizophrenia compared to controls. Thus, the selective diffusion of bovine milk casein and wheat gluten antibodies between serum and CSF in schizophrenia may be the function of a low-level anatomical barrier dysfunction or altered CSF flow rate, which may be transient in nature.

1. Introduction

A variety of central nervous system (CNS) and peripheral biomarkers of inflammatory processes are altered in schizophrenia, including C-reactive protein, cytokines, kynurenine pathway metabolites, autoantibodies, antibodies to microbial agents and other extrinsic antigens, gastrointestinal (GI) and white matter functions or morphologies (Dickerson et al., 2013; Drexhage et al., 2010; Fillman et al., 2013, 2014; Gibney and Drexhage, 2013; Leonard et al., 2012; Linderholm et al., 2012; Miller et al., 2011, 2012; Monji et al., 2013; Muller, 2014; Muller et al., 2012; Severance et al., 2012a, 2013, 2014; Torrey et al., 2012; Yolken and Torrey, 2008). However, the mechanisms underlying variable immune activation observed in schizophrenia populations are poorly understood, because the immune pathology differs in scope and intensity from classic inflammatory diseases of the CNS, such as viral encephalitis and multiple sclerosis (Bechter, 2013; Bechter et al., 2010). It has been difficult to fully disentangle the contribution of antipsychotics to changes in inflammatory indices in schizophrenia, but a number of studies performed in recent onset and antipsychotic-naïve patients suggests that evidence of specific immune activation can be seen early in the disease, even before medication is administered (Beumer et al., 2012; Drexhage et al., 2010, 2011; Leonard et al., 2012; Miller et al., 2012; Mondelli and Howes, 2014; Severance et al., 2012a,b, 2013; Steiner et al., 2012; Stojanovic et al., 2014).

In schizophrenia, a subset of individuals may be particularly sensitive to immune activation following the digestion of certain dietary proteins, such as wheat gluten and bovine milk casein (Cascella et al., 2011; Dickerson et al., 2010; Dohan, 1979, 1981; Dohan and Grasberger, 1973; Dohan et al., 1969; Lachance and

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McKenzie, 2014; Niebuhr et al., 2011; Reichelt, 1991; Reichelt et al., 1981, 1995; Severance et al., 2010a). The proteins, gluten and casein, are hydrolyzed in the GI tract into hundreds to thousands of peptides, some of which have been shown to have opioid-like properties and are referred to as exorphins (Boutrou et al., 2013; Dohan, 1979, 1980, 1988a,b; Prandi et al., 2014; Reichelt, 1991, 1994; Reichelt et al., 1981, 1985, 1995, 2012). The immunomodulatory potential of these exorphins is not well-understood, with observations that among the repertoire of digested peptides, some have pro-inflammatory and others have anti-inflammatory effects (Aihara et al., 2014; Barnett et al., 2014; Haq et al., 2014; Kaminski et al., 2007). The mechanisms by which peptides derived from wheat gluten and bovine milk casein or the associated immune response might be pathogenic in schizophrenia are not known. Older studies report that casein-related exorphins are present in the CSF of individuals with postpartum depression and schizophrenia (Lindstrom et al., 1984, 1986). Presumably, exorphins located in the CSF would lead to intrathecal production of antibodies against these antigens. Intrathecal IgG production directed at specific antigens occurs in viral encephalitis, and this IgG abundance is reflected by a lack of congruence between CSF and serological IgG. In patients with multiple sclerosis, CSF immune profiles are often characterized by the chronic intrathecal production of polyspecific IgG, and similarly, serological and CSF IgG levels do not correlate (Jacobi et al., 2007; Stangel et al., 2013). These dynamics are complicated, but their evaluation can lend insight to the degree that CSF- and brain-related endothelial barrier or flow defects and the immune response to dietary antigens might be involved in the pathogenesis of schizophrenia.

In the present study, we sought to quantify the relative differences in food protein-related antibody levels and examine the possibility of an intrathecal source of antibody production in patients with first episode schizophrenia, the majority of whom were antipsychotic-naïve, compared to non-psychiatric controls. We measured IgG to bovine milk casein and wheat gluten in matched serum and CSF samples and compared antibody levels to standard indices of CSF barrier dysfunction and localized CNS antibody generation.

2. Materials and methods

2.1. Participants

Methods for identifying and characterizing individuals with a first episode of schizophrenia according to criteria defined by DSM-IV have been previously described (Leweke et al., 2004). A total of 105 individuals with first episode schizophrenia were included. Seventy-five of these individuals were antipsychotic-naïve and 30 were currently receiving antipsychotic medication. Only DSM-IV diagnoses of 295.1–295.3 were included. Sixty-one healthy volunteers served as the control group. Individuals were excluded from the study if they had a relevant comorbidity such as heart disease, liver cirrhosis, known immune-mediated disease (such as multiple sclerosis), or a history of substance dependence. Only individuals who were less than 50 years of age were included. Demographic data regarding age and sex are listed in Table 1. Previous analyses of this study population indicated that study individuals were also generally homogeneous in terms of socioeconomic characteristics, geography and ethnicity and did not differ significantly with respect to body mass index (Hayes et al., 2014; Leweke et al., 2004). Informed written consent was obtained from all study participants. Protocols for sample collection and analyses were approved by the ethics committee at the University of Cologne, Heidelberg University and Johns Hopkins University, in accordance with the Declaration of Helsinki.

Table 1
Study population demographics.

	n	Age Mean years ± SEM[a]	Female *n* (%)
Controls	61	27.16 ± 0.65	31 (50.8)
First episode schizophrenia	105	28.62 ± 0.78	38 (36.2)
Antipsychotic-naive	75	28.53 ± 0.92	26 (34.7)
Antipsychotic-positive	30	28.87 ± 1.53	12 (40.0)

[a] SEM refers to standard error of the mean.

Serum and CSF samples were collected according to the methods described previously (Leweke et al., 2004). Lumbar punctures were performed at the same time of day using a non-traumatic lumbar puncture procedure. Serum samples were collected concurrently. Serum and CSF analyses performed at time of acquisition included measures of albumin, total IgG and glucose. Samples were then frozen and stored at −80 °C.

2.2. Laboratory procedures

The enzyme-linked immunosorbent assays (ELISAs) to detect bovine casein-, and wheat gluten-related IgG have been previously described (Severance et al., 2012a,b). Whole casein was purchased from Sigma–Aldrich (St. Louis, MO, U.S.A.). Whole gluten was extracted from the wheat cultivar Cheyenne as previously described (Samaroo et al., 2010). In brief, for both the casein and gluten immunoassays, plate wells were incubated with 100 ng protein in 50 µl carbonate buffer (0.05 M carbonate–bicarbonate, pH 9.6; Sigma–Aldrich, St. Louis, MO, U.S.A.) overnight at 4 °C, and plates were blocked for 1 h at 37 °C with 1% (wt/vol) human serum albumin (Sigma–Aldrich, St. Louis, MO, U.S.A.) in PBS. Plates were then incubated with serum samples diluted 1:200 and CSF samples diluted 1:10 for 2 h at 37 °C. Plates were washed and incubated with peroxidase-conjugated goat-anti-human IgG secondary antibodies for 30 min at 37 °C (Southern Biotech, Birmingham, AL, U.S.A.). A 2,2′-azino-di-(3-ethylbenzthiazoline-6-sulfonate) and 0.02% hydrogen peroxide solution (KPL Protein Research Products, Gaithersburg, MD, U.S.A.) was added for color development, and absorbance was measured at 405 nm, with a reference wavelength of 490 nm, in an automated microtiter plate reader (Molecular Devices, Menlo Park, CA, U.S.A.).

2.3. Statistical analyses

Plate-to-plate variation of the food antigen IgG was corrected by mean-normalizing each plate (i.e. mean absorbances of each plate equaled a value of "1"). Both mean-normalized and non-mean-normalized data for food antigen IgG were subjected to statistical analyses. Background reactivity of blank wells was subtracted from plate measurements for the non-mean-normalized dataset. When results were consistent across both datasets, the mean-normalized data were used to depict representative results in the relevant tables and figures. Quantitative biomarker levels (antibodies, glucose, albumin) were compared between study groups using two tailed *t*-tests. Multiple linear regression models including age and sex were implemented to assess biomarker inter-correlations and associations of biomarkers with other variables. Bonferroni correction of multiple comparisons resulted in p values less than 0.0125 (0.05/4) to be considered statistically significant. Information regarding albumin, total IgG and glucose in body fluids was available for only a subset of individuals in each group, and these sample sizes are listed in the results section.

The albumin and total IgG measures and interpretations described here are considered standard indices of CSF activity (Kirch et al., 1992; Mundt and Shanahan, 2011; Reiber, 1994;

Reiber and Peter, 2001; Schliep and Felgenhauer, 1978; Stangel et al., 2013; Tibbling et al., 1977). The albumin ratio was calculated as [CSF albumin/serum albumin] with albumin ratios above 9 considered indicative of blood–brain or blood–CSF anatomical barrier or CSF flow dysfunction. The total IgG ratio was also calculated [CSF IgG/serum IgG] for comparative purposes. For determination of intrathecal antibody production based on the broader total IgG and albumin abundances, a CSF IgG index was calculated as [(CSF IgG/serum IgG) × (serum albumin/CSF albumin)]. This ratio is a measure of intrathecal antibody production that is corrected for CNS barrier defects detected by altered albumin ratios. A CSF IgG index level between 0.3 and 0.7 is considered normal (Kirch et al., 1992; Mundt and Shanahan, 2011; Reiber, 1994; Reiber and Peter, 2001; Schliep and Felgenhauer, 1978; Stangel et al., 2013; Tibbling et al., 1977).

The Antibody Index (AI) to measure the intrathecal production of antigen-specific antibodies was calculated as follows: [(specific CSF IgG/specific serum IgG)/(total CSF IgG/total serum IgG)] (Mundt and Shanahan, 2011; Reiber and Peter, 2001; Schrodl et al., 2004). The quantification of an AI when applied properly is a highly sensitive measure of the CSF antibody response and is intended for aiding the accurate and precise documentation of infectious disease diagnoses. Our application of the AI for use in the assessment of food antigen antibodies must be considered preliminary. The laboratory assays that we used to detect relative measures of IgG to food antigens were homemade and did not provide measures of absolute concentrations of antigen-specific IgG in the studied biofluids. To ascertain a preliminary indication of a possible intrathecal production of food-related antibodies, we used the non-mean-normalized data in our analyses to formulate a numerical AI value, because the data normalization procedure would otherwise effectively eliminate differences in serum IgG compared to CSF IgG. To minimize the reporting of false-positive AI measures, we considered an AI above "2" as suggestive of possible intrathecal antibody production, instead of the more often utilized "1.5" value (Schrodl et al., 2004; Terryberry et al., 1998). Differences in AI positivity between diagnostic groups were evaluated with chi-square tests.

Statistical analyses were performed with STATA version 12 (STATA Corp. LP, College Station, Texas, U.S.A.).

3. Results

3.1. Quantitative levels of casein and gluten IgG antibodies in serum and CSF

Plate mean-normalized data are shown in Table 2 for both biospecimen types. A number of quantitative differences between case and control groups were recorded for the CSF samples. We found a significant increase of anti-casein IgG in the CSFs of individuals who were antipsychotic-naïve (mean ± standard error of the mean: 0.48 ± 0.11) compared to casein antibody levels in the CSFs of the control group (0.13 ± 0.03, $t = 2.75$, $p \leqslant 0.007$), when evaluating the non-mean-normalized data. Using both the non-mean-normalized and mean-normalized datasets, there was a significant increase of anti-gluten IgG in the CSFs of individuals who were antipsychotic-positive compared to those who were antipsychotic-naïve (Table 2; $p \leqslant 0.006$). In serum samples, IgG levels between patient diagnostic groups were generally not different.

Table 3
Serological casein and gluten IgG correlate with CSF casein and gluten IgG in schizophrenia.

	n	R^2	Coefficient	95th% CI[a]	*p*-value
Casein					
Controls	61	0.05	−0.16	−0.40–0.08	0.44
First episode schizophrenia	105	**0.55**	**0.40**	**0.32–0.48**	**0.0001**
Antipsychotic-naive	75	**0.64**	**0.38**	**0.30–0.46**	**0.0001**
Antipsychotic-positive	30	0.30	0.46	0.15–0.78	0.03
Gluten					
Controls	61	0.06	−0.30	−0.70–0.11	0.33
First episode schizophrenia	105	**0.34**	**0.50**	**0.35–0.66**	**0.0001**
Antipsychotic-naive	75	**0.19**	**0.36**	**0.07–0.64**	**0.002**
Antipsychotic-positive	30	**0.75**	**0.65**	**0.49–0.81**	**0.0001**

Bolded values were statistically significant and Bonferroni-corrected at $p \leqslant 0.0125$.
[a] CI refers to confidence interval.

3.2. Correlations between serum and CSF levels of antibodies to dietary antigens

To examine if food-related antibody levels in serum were predictive of CSF levels, we used multiple linear regressions corrected for age and sex. We found in both the non-mean-normalized and mean-normalized datasets that serum anti-casein IgG and serum anti-gluten IgG levels were correlated well with CSF levels of these antibodies in schizophrenia only (mean-normalized data, Table 3, Fig. 1, $p \leqslant 0.0001$–0.002). Serum anti-casein IgG was significantly correlated with CSF anti-casein IgG only in the antipsychotic-naïve group ($p \leqslant 0.0001$), although a trend toward significance was observed in the antipsychotic-positive group ($p \leqslant 0.03$). Similarly, anti-gluten serum IgG corresponded with CSF levels in both schizophrenia groups ($p \leqslant 0.0001$–0.002). Serum levels of IgG to casein and gluten were not significantly correlated with the respective CSF antibody levels in the control group.

3.3. Quantitative levels of albumin, total IgG and glucose in serum and CSF

We evaluated a series of basic serum and CSF indices to characterize serum to CSF diffusion dynamics in a set of samples for which we had these data available (sample sizes for this subset analysis are listed in Table 4). Quantitative levels of albumin and total IgG were significantly lower in serum from the schizophrenia groups compared to controls (Table 4, $p \leqslant 0.0001$–0.0004), but no inter-group

Table 2
Quantitative levels of casein and gluten IgG in serum and CSF.

	n	Serum		CSF	
		Casein Mean ± SEM[a]	Gluten Mean ± SEM	Casein Mean ± SEM	Gluten Mean ± SEM
Controls	61	1.03 ± 0.17	1.03 ± 0.18	0.83 ± 0.19[b]	0.89 ± 0.12
First episode schizophrenia	105	1.02 ± 0.10	0.81 ± 0.12	1.01 ± 0.18	0.80 ± 0.13
Antipsychotic-naive	75	1.04 ± 0.12	0.80 ± 0.14	**1.04 ± 0.24**[b]	0.59 ± 0.10[c]
Antipsychotic-positive	30	0.96 ± 0.18	0.84 ± 0.26	0.95 ± 0.20	**1.34 ± 0.34**[c]

Bolded values were statistically significant and Bonferroni-corrected at $p \leqslant 0.0125$.
[a] SEM refers to standard error of the mean.
[b] Mean-normalized data shown were not statistically significant; Non-mean-normalized data (see text) were statistically significant, $t = 2.75$, $p \leqslant 0.007$.
[c] Mean- and non-mean-normalized data were statistically significant, $t = 2.79$, $p \leqslant 0.006$, antipsychotic-positive compared to antipsychotic-naïve.

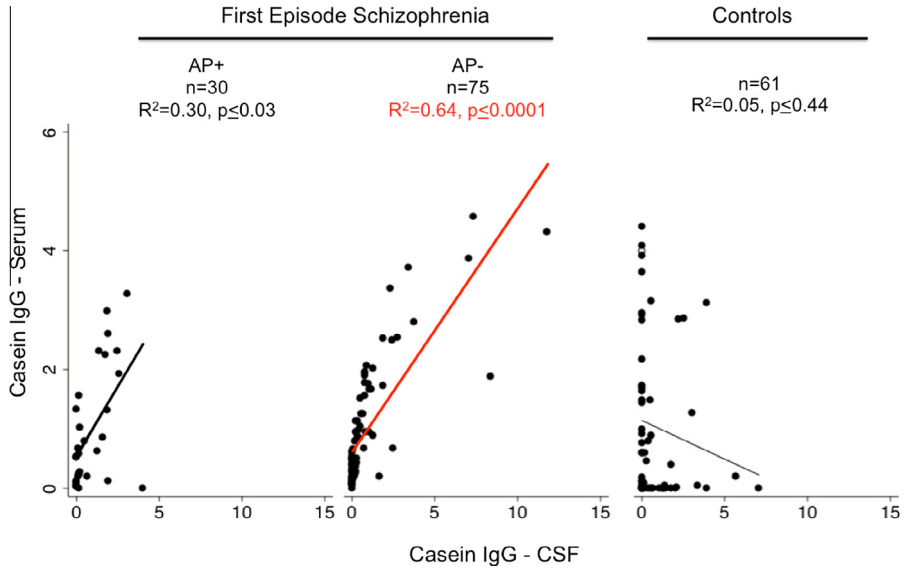

Fig. 1. Serum levels of anti-casein IgG are predictive of CSF IgG levels in schizophrenia. Significant correlations of serological anti-casein IgG with CSF anti-casein IgG are indicated in red. Patterns for serum vs CSF anti-gluten IgG were similar, and statistical data for antibodies to both antigens can be found in Table 3. These data implicate a diffusion of serum anti-casein antibodies to the CSF in schizophrenia, which was not present in controls. AP+ refers to antipsychotic-positive and AP− refers to antipsychotic-naïve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Quantitative levels of basic serum and CSF indices.

Index	Serum			CSF		
	n	Mean ± SEM[a]	*t*, *p*-value[b]	*n*	Mean ± SEM	*t*, *p*-value[b]
Controls						
Albumin	60	4786.38 ± 59.03	–	60	19.82 ± 0.99	–
Glucose	60	86.52 ± 1.83	–	60	58.17 ± 0.57	–
IgG	60	1233.87 ± 34.42	–	60	2.35 ± 0.11	–
First episode schizophrenia						
Albumin	54	4361.20 ± 65.23	**−4.85, 0.0001**	54	23.85 ± 1.44	2.35, 0.02
Glucose	32	**97.16 ± 2.93**	**3.23, 0.002**	52	**65.92 ± 1.86**	**4.23, 0.0001**
IgG	54	**1023.52 ± 30.48**	**−4.53, 0.0001**	54	2.65 ± 0.18	1.45, 0.15
Antipsychotic-naive						
Albumin	40	**4435.10 ± 75.16**	**−3.71, 0.0004**	40	23.42 ± 1.50	2.09, 0.04
Glucose	24	95.17 ± 3.39	2.40, 0.02	38	**67.00 ± 2.48**	**4.21, 0.0001**
IgG	40	**1015.10 ± 36.69**	**−4.23, 0.0001**	40	2.53 ± 0.18	0.91, 0.36
Antipsychotic-positive						
Albumin	14	**4150.07 ± 117.75**	**−4.72, 0.0001**	14	25.09 ± 3.60	1.97, 0.05
Glucose	8	**103.13 ± 5.70**	**3.07, 0.003**	14	**63.00 ± 1.36**	**3.58, 0.0006**
IgG	14	1047.57 ± 54.88	−2.45, 0.02	14	2.98 ± 0.45	1.99, 0.05

Bolded values were statistically significant and Bonferroni-corrected at $p \leqslant 0.0125$.
[a] SEM refers to standard error of the mean; units are mg/dL.
[b] Test comparisons were schizophrenia groups vs. controls.

differences were present in CSF. In both serum and CSF, quantitative levels of glucose were significantly higher in the schizophrenia groups compared to controls (Table 4, $p \leqslant 0.0001$–0.003). Antibodies to neither casein nor gluten were significantly correlated with any of these basic serum or CSF indices.

3.4. Intrathecal antibody production based on albumin and total IgG measures

To examine a possible role of intrathecal production of antibodies, CNS endothelial barrier defects or altered CSF flow in the disease state, we calculated the CSF-to-serum ratios of albumin and total IgG. We found that the CSF-to-serum albumin ratios were significantly elevated in both antipsychotic-naïve (mean ± standard error of the mean, 5.26 ± 0.21, $p \leqslant 0.003$) and antipsychotic-positive (6.09 ± 0.91, $p \leqslant 0.002$) schizophrenia patients compared to controls (4.16 ± 0.21; Fig. 2). CSF-to-serum total IgG ratios were also significantly elevated in the schizophrenia groups (antipsychotic-naïve, 2.53 ± 0.16, $p \leqslant 0.002$; antipsychotic-positive 2.92 ± 0.44, $p \leqslant 0.001$) compared to controls (1.95 ± 0.10; Fig. 2).

Serum albumin was correlated to CSF albumin in the individuals who were antipsychotic-naïve only (Fig. 3, $p \leqslant 0.001$). Serum IgG was correlated to CSF IgG in both the antipsychotic-naïve and control groups (Fig. 4; $p \leqslant 0.003$–0.01). The CSF-to-serum albumin ratio was significantly correlated to the CSF-to-serum IgG ratio in all groups (Fig. 2, $p \leqslant 0.0001$). The CSF index that measures intrathecal IgG production corrected for albumin diffusion across barriers was not significantly different between groups (0.48 ± 0.01 for both schizophrenia groups; 0.47 ± 0.01 for controls) and was within the numerical range of diffusion quotients that are considered normal: 0.30–0.70 (Mundt and Shanahan, 2011). These indices were not correlated with age or sex.

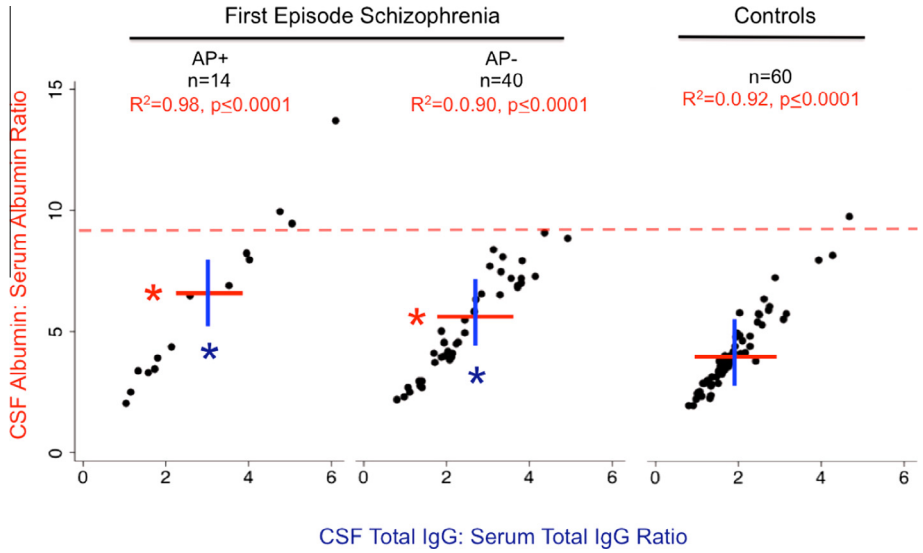

Fig. 2. Measures of CSF-to-serum albumin and total IgG levels are elevated in schizophrenia. Solid horizontal red line refers to mean albumin ratios. Dashed horizontal red line refers to upper limit of numerical range considered normal for barrier integrity. Solid vertical blue line refers to mean IgG ratios. Mean levels and standard errors can be found in the main text. Asterisks (*) refer to significant differences in mean levels of cases compared to controls. Significant regression and *p*-values from correlations of albumin ratios with IgG ratios are indicated in red text. Elevated CSF-to-serum albumin and IgG ratios in schizophrenia implicate the presence of CSF barrier or flow defects. AP+ refers to antipsychotic-positive and AP− refers to antipsychotic-naïve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

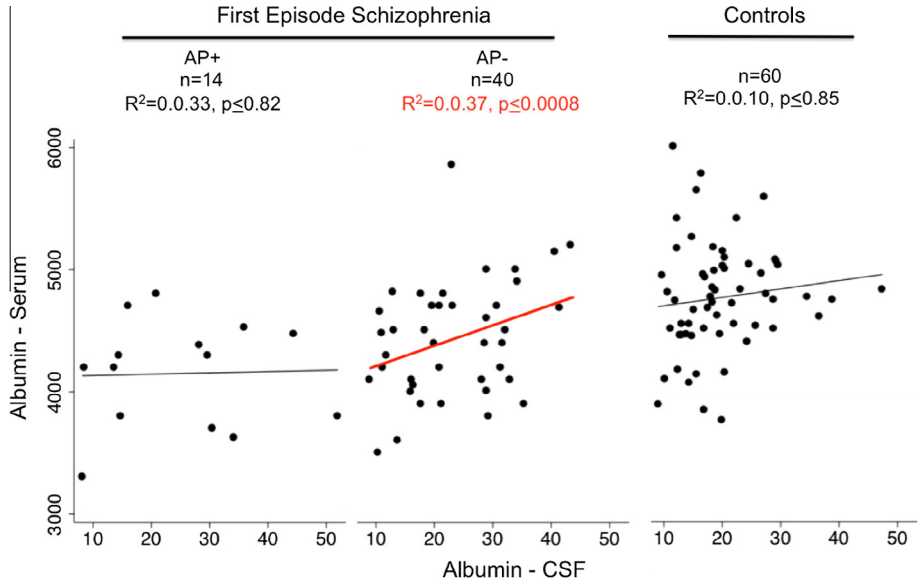

Fig. 3. Serum levels of albumin are predictive of CSF levels in schizophrenia. Significant regression and *p*-values from correlations are indicated in red. AP+ refers to antipsychotic-positive and AP− refers to antipsychotic-naïve. The significant correlation of serum albumin with CSF albumin only in the AP− schizophrenia group supports the presence of CSF anatomical barrier or flow defects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. Intrathecal antibody production of casein and gluten antibodies

Preliminary AI measures of food antigen-specific IgG could be calculated in a subset of individuals who had non-zero values in fraction denominators. For anti-casein IgG, positive AI values ranged from 2.6% (1 of 39) in the antipsychotic-naïve group, 7.7% (1 of 13) in the antipsychotic-positive group, and 12.5% (5 of 40) in the controls. For anti-gluten IgG, positive AI values ranged from 9.1% (3 of 33) in the antipsychotic-naïve group, 10% (1/10) in the antipsychotic-positive group, and 29.7% (11 of 37) in the control group. Differences in AI positivity between cases and controls were not statistically significant following Bonferroni correction, although there was a trend toward increased AI positivity for gluten in the controls compared to cases (chi-square = 5.45, $p \leqslant 0.02$).

4. Discussion and conclusions

4.1. Overview

The primary finding of our study was the strong correlation between serum and CSF antibodies to dietary antigens in individuals with schizophrenia, a pattern of correspondence that was not present in control individuals. These data suggest a less restrictive

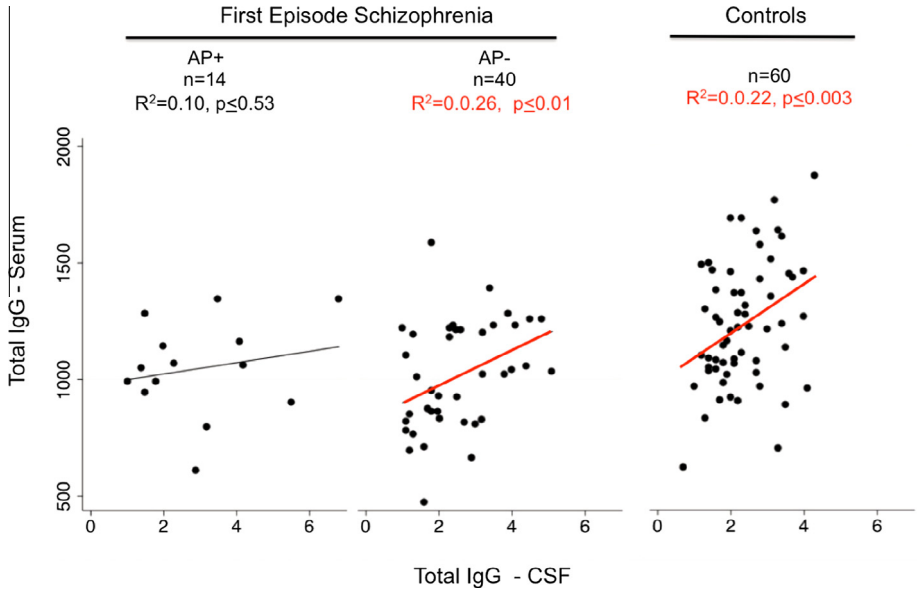

Fig. 4. Serum total IgG levels are correlated with CSF IgG in both schizophrenia and controls. Significant regression and *p*-values from correlations are indicated in red. AP+ refers to antipsychotic-positive and AP− refers to antipsychotic-naive. The significant correlation of serum total IgG with CSF IgG in both AP− and control groups provides preliminary evidence of a lack of intrathecal antibody production. The absence of significant differences in two follow-up measures, the CSF IgG Index and specific Antibody Index (not shown; see main text), suggests that casein and gluten IgG in the CSF may have predominantly originated in serum in this sample set. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diffusion of antibodies to casein and gluten from the serum to CSF in people with schizophrenia. These food-derived antibody dynamics contrasted to those of total IgG, where serum levels were generally predictive of CSF levels in both cases and controls. The mechanistic basis of this antigenic specificity is not known. In preliminary tests, we found that intrathecal IgG production directed against food antigens occurred in a small number of both cases and controls, but the differences between diagnostic groups were not statistically significant. Disease-associated elevations in albumin ratios were consistent with the hypothesis of a low level of endothelial barrier dysfunction in schizophrenia, perhaps to a degree that might result in subtle or transient dysregulation of barrier channels. An increased albumin ratio also can be indicative of a decreased CSF flow rate, a dysfunction with numerous physiological causes (Reiber, 1994; Whedon and Glassey, 2009). For example, CSF flow patterns can be disrupted by degenerative and pathological CNS features such as calcification at the choroid plexus, arachnoid cysts and decreased brain volumes, all of which are conditions that have been previously associated with the pathophysiology of psychoses and schizophrenia (Arango et al., 2012; Kuloglu et al., 2008; Marinescu et al., 2013; Narr et al., 2003; Reiber, 1994; Rimol et al., 2012; Sandyk, 1993; Shiga et al., 2012; Veijola et al., 2014; Whedon and Glassey, 2009).

4.2. Quantitative differences of casein and gluten antibody levels in serum and CSF

The study of antibodies directed at food antigens in schizophrenia has a long history largely rooted in observations of epidemiological overlaps with celiac disease, a debilitating autoimmune gut pathology that develops following the ingestion of wheat gluten (Chen et al., 2012; Dohan, 1966a,b; Eaton et al., 2004, 2006). People with schizophrenia can have up to 3–4 times the amount of anti-gluten antibodies than normal control individuals and this gluten antibody link has been replicated in a number of studies (Cascella et al., 2011; Dickerson et al., 2010; Jin et al., 2010; Lachance and McKenzie, 2014; Okusaga et al., 2013; Reichelt and Landmark, 1995; Sidhom et al., 2012). Similarly, antibodies directed against bovine milk casein may also be increased in psychiatric illnesses, in some cases evident up to 2 years prior to diagnosis (Niebuhr et al., 2011; Severance et al., 2010a,b). In our study, we detected an elevation in anti-casein IgG in the CSFs of individuals with schizophrenia who were antipsychotic-naïve compared to controls, whereas serum antibodies did not significantly differ between diagnostic groups. These contrasting serological findings could be due to cohort variations in diet, ethnic or gender compositions, geography or timeframes when samples were collected, all of which are factors that contribute to variability in measures of the food-related immune response, both in controls and in schizophrenia. The fact, however, that casein antibodies were elevated in the CSF of individuals with schizophrenia compared to controls in our study lends credence to a possible pathological role of these antibodies in the CNS. In several reports, a cross-reactivity of anti-gliadin antibodies with brain proteins has been described (Alaedini et al., 2007; Briani et al., 2008; Hadjivassiliou et al., 2002). This possibility is consistent with other findings of immune sensitivities to food antigens, and especially gluten, in a variety of other brain diseases and conditions, including bipolar disorder, ataxia, epilepsy and autism (Burk et al., 2001; Chinnery et al., 1997; Dickerson et al., 2011; Lau et al., 2013; Severance et al., 2010b; Vojdani et al., 2004). Diets that employ removal of casein and/or gluten dietary antigens have met with modest success in terms of behavioral and cognitive amelioration in people with autism and schizophrenia, especially when individuals with gut and immune-related symptoms are pre-identified as suitable candidates for study inclusion (Jackson et al., 2012; Pedersen et al., 2014; Whiteley et al., 2010, 2012).

4.3. Evidence for blood–CSF anatomical barrier dysfunction, CSF flow disruption and intrathecal antibody production

In our study, control individuals who had high serum IgG antibodies against casein and gluten did not have corresponding elevations of these antibodies in their CSF, and this pattern differs from the IgG dynamics observed in individuals with schizophrenia. Our results suggest an intact regulation in these control individuals, which allows a less restricted diffusion of antibodies across the

blood–CSF barrier. The standard serum- and CSF-related indices used to detect CNS production of IgG, endothelial barrier defects, and CSF flow dysregulation were generally within ranges found in individuals without neurological or psychiatric disorders. However, even within these normal ranges, individuals with schizophrenia compared to controls had significantly elevated levels of the following: (1) serum and CSF glucose, (2) CSF-to-serum albumin ratio, and (3) CSF-to-serum total IgG ratio. Schizophrenia-associated glucose elevations in the CSF have been reported previously and were thought to reflect gluco-regulatory processes occurring in the brain, which were also independent of antipsychotic medications (Holmes et al., 2006). In our study, elevations in the albumin ratios and significant correlations of CSF albumin with serum albumin only in the antipsychotic-naïve group suggests a low-level dysfunction of CNS-related barriers or altered CSF flow rate (Reiber, 1994). The CNS does not synthesize albumin; therefore, any albumin found in the CNS must be transported across the blood–brain or blood–CSF barrier (Tibbling et al., 1977).

Measures of the CSF IgG index and the specific AI index did not support the hypothesis of intrathecal IgG production associated with schizophrenia in this sample set, although our preliminary indices suggest that this process occurred in both cases and controls. There was actually a trend toward an increased gluten AI in controls compared to cases, but the statistics did not survive multiple comparison correction. Based on an absent correlation of food antigen antibodies between serum and CSF in controls, a possibly increased intrathecal antibody production in controls would be consistent with the patterns that we observed. Based on the well-correlated IgG in serum vs CSF in schizophrenia only, a permeability or flow defect in the cases also seems a reasonable interpretation of the results that we obtained. These findings are similar to the results of Bauer and Kornhuber (1987) who found evidence for increased blood–CSF permeability but not local CNS IgG synthesis in patients with schizophrenia (Bauer and Kornhuber, 1987). Bechter et al. (2010) and Kirch et al. (1985), on the other hand, both detected a low level of endogenous CNS IgG production in addition to increased barrier permeability measures in patients with schizophrenia (Bechter et al., 2010; Kirch et al., 1985). In bipolar disorder, Zetterberg et al. (2014) recently reported elevated CSF-to-serum albumin ratios in people who were receiving antipsychotic treatment compared to controls (Zetterberg et al., 2014). We also observed the highest levels of this ratio in patients with schizophrenia who were receiving antipsychotics; however, those with schizophrenia who were antipsychotic-naïve also had significantly elevated levels compared to controls, suggesting that the questionable blood–CSF interface dysfunction is not just related to medication. An effect of antipsychotic medication on CSF IgG was evident in our study by significantly elevated anti-gluten CSF antibodies in patients who were receiving antipsychotics compared to those who were not.

4.4. Anatomical impedances that might impact CSF barrier and flow function

The primary anatomical sites of the blood–CSF barrier are the choroid plexus and arachnoid membrane (Laterra et al., 1999). The choroid plexus is not well-studied in schizophrenia, but one researcher, Rudin, reviewed the role of this CSF–blood interface and how the choroid plexus may be an important transport locale protecting the limbic system of the brain (Rudin, 1980, 1981a,b). Rudin also suggested that any dysfunction of the choroid plexus might reconcile viral and exogenous peptide hypotheses of disease causation, as infectious agents and exogenous peptides might easily pass across this barrier perhaps in genetically susceptible individuals (Rudin, 1981b). Others report that calcification of the choroid plexus can be associated with symptoms of psychosis and cognitive deficiencies, presenting much like schizophrenia (Marinescu et al., 2013; Sandyk, 1993). The role of arachnoid membrane dysfunction in schizophrenia is also an understudied subject; however, a series of reports link the presence of arachnoid cysts to schizophrenia-like symptoms (Kuloglu et al., 2008; Narr et al., 2003; Shiga et al., 2012).

4.5. Gene and environmental interactions of immune dysfunction and barrier permeability in schizophrenia

Although schizophrenia has a strong heritable component, it is a disorder thought to result from an interaction of both genetic and environmental factors (Demjaha et al., 2012; Modinos et al., 2013; Tsuang, 2000; van Os et al., 2014). A replicated susceptibility locus that is consistent with a gene by environment etiology of schizophrenia is the 6p21 region encoding the major histocompatibility complex and human leukocyte antigen genes (Corvin and Morris, 2014; Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009). This family of genes is important in immune system functioning and coordinating the immune response to a variety of antigens (Corvin and Morris, 2014). A number of cellular barrier proteins and related biological pathways that have shown genetic associations with schizophrenia include the tight junction protein claudin-5, cytoskeletal elements such as actin, haptoglobin and nitric oxide synthetase (Burghardt et al., 2014; Hall et al., 2014; Horvath and Mirnics, 2014; Maes et al., 2001; Sun et al., 2004; Wan et al., 2007; Wei and Hemmings, 2005; Yang et al., 2006; Ye et al., 2005; Zhao et al., 2014). Endothelial barriers can also be rendered permeable by pathogens, toxins and stress and thus a genetically programmed immune and/or barrier defect could be compounded by exposure to these environmental triggers (Collins and Bercik, 2009; Lambert, 2009; Soderholm and Perdue, 2001). In a scenario that is relevant to our results, we can hypothesize that the coupling of a genetic immune defect with a genetic or environmentally-derived epithelial or endothelial barrier abnormality could enable antigens such as the food exorphins to more readily cross into circulation and trigger an immune response. In the presence of an immune defect, these exorphins may evade detection or create a state of hyper-immune activation, and they or antibodies directed against them could gain access to the CNS, again by faulty barrier processes, given the similarities of the gut and brain endothelial cytoarchitectures (Deli, 2009; Jong and Huang, 2005; Laterra et al., 1999). It is also conceivable that the initial disturbance could occur prenatally with the antigens or the resulting immune response impacting neuronal migration; subsequent exposures could then act to exacerbate CNS symptoms. Interestingly, gluten peptides may be capable of independently altering endothelial barriers through a direct effect on the tight junction protein, zonulin (Clemente et al., 2003; Fasano, 2012; Lammers et al., 2008; Thomas et al., 2006).

4.6. Study limitations

Our study has a number of limitations that might impact the extent to which our data can be interpreted. The calculations that we performed for determining the role of intrathecal antibody production of casein and gluten antibodies can only serve as a rough estimate. Follow-up studies should apply a comprehensive approach to address this question and include the use of ELISA kits certified for diagnostic purposes and absolute immunoglobulin quantification. This methodology would further benefit from inclusion of measures of oligoclonal IgG and of individual immunoglobulin classes (including IgA and IgM). If recruitment strategies allowed, future studies might ensure that the control group is not underrepresented, and ideally incorporate a case–control matched pair, prospective study design. Additional demographic and clinical

information including cognitive function and symptom severity could be collected and tested for correlations with physiological markers. Our study design currently does not allow us to assign causality of the studied antibodies and other markers with the development or resolution of the signs and symptoms of schizophrenia. Furthermore, it is not clear based on the current cross-sectional study structure if these barrier defects or immune dysregulation are transient or inherently permanent pathologies. Thus, a longitudinal aspect of sample collection coupled with a surrogate measure of endothelial barrier defects could help address the temporal variation that might be associated with these markers.

4.7. Conclusions

In conclusion, our data support the concept that CSF-related endothelial and flow abnormalities may be present in individuals with schizophrenia and that the dissemination of food-derived antibodies may be positively impacted by this dysfunction. A lack of evidence for the local CNS production of food-related IgG implicates a pathological scenario involving CSF barrier or flow defects. Peripherally-derived casein and gluten IgG may enter a transiently permeable blood–CSF or blood–brain barrier and be directly pathogenic to the brain, perhaps binding to epitopes on functionally important brain proteins such as neuronal synapsin (Alaedini et al., 2007). Future work is required to examine this hypothesis as well as to evaluate the function and stability of the choroid plexus and arachnoid membrane in post-mortem and imaging studies in schizophrenia. Results from studies in the fields of stroke, brain injury and liver failure, have shown that such compounds as melatonin, idazoxan, an imidazoline 2 receptor ligand, and inhibitors of matrix metalloproteinases may protect against blood–brain barrier and choroid plexus pathologies induced by a variety of methods in cell culture experiments and rodent models (Chen et al., 2013; Turgut et al., 2007; Verma et al., 2010; Wang et al., 2014).

Thus, based on this work, therapies aimed to remove the antigenic source and to normalize endothelial barrier functions may be applicable treatment modalities to explore for safety and efficacy trials in schizophrenia.

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