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Elevated anti-gliadin IgG antibodies are related to treatment resistance in schizophrenia

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1. Introduction

Schizophrenia is currently believed to be a syndrome comprising several distinct diseases [1,2]. Although the pathogenesis of schizophrenia is unclear, several studies suggest that it is associated with immunologic factors [3–6]. Recent studies report that approximately 20–30% patients with schizophrenia are positive for anti-gliadin IgG (AGA-IgG) compared to <10% in controls [7–9], and have shown that AGA-IgG positive patients of schizophrenia could be a subgroup. Additionally, the patients with recent-onset or multi-episode schizophrenia had a higher prevalence of AGA-IgG compared with controls [10]. Positive symptoms of schizophrenia were lower in the AGA-IgG positive patients [11].

Recently, AGA-IgG has been presented as an immunologic marker of gluten sensitivity (GS). Gluten is a protein in grains such as wheat, barley, and rye. Its elasticity and flexibility are important in making wheat flour-processed products such as noodles, bread, and pasta. GS is a syndrome characterized by several intestinal, extra-intestinal, and psychological symptoms related to the ingestion of gluten [12,13], distinct from celiac disease (CD) and wheat allergy [14,15]. A variety of clinical features are associated with GS, such as abdominal pain, constipation, diarrhea, alternating bowel habits, headache, skin rash, joint and muscle pain, foggy brain, tiredness, anxiety, and depression [14]. The symptoms are worsening with gluten ingestion and improved by gluten-free diet (GFD). Indeed, several studies have suggested that GS is closely linked to neuropsychiatric disorders [16,17].

Currently, the prevalence of CD has been estimated as approximately 1% in the general population and that of GS has been reported widely ranging from 0.55% to 6% in Western populations overall [12,18,19]. In Japan, the prevalence of CD is reported as 0.05–0.7%, and while that of GS remains unclear [20,21], it can be assumed that GS may be more prevalent than CD in the general Japanese population, as reported in Western countries.

Few studies have been conducted to investigate clinical features of patients with schizophrenia having GS worldwide. In Japan, there are no epidemiological data on GS in the general population nor in those with psychiatric disorders. Furthermore, demographic profiles and clinical features of Japanese patients with schizophrenia having GS have yet to be elucidated.

For our study, we hypothesized Japanese patients with schizophrenia being more likely to have GS compared with control subjects. Additionally, patients with GS may be characterized as having more severe psychiatric symptoms and poorer treatment responses than those without sensitivity to gluten. Therefore, this study aimed to investigate the prevalence of immunological GS in Japanese patients with schizophrenia. We also sought to examine the relationship between immunological GS and clinical features as well as treatment profiles associated with schizophrenia.

2. Methods

2.1. Study participants

We studied Japanese patients with schizophrenia and age-, sex-matched Japanese control subjects without any history of psychiatric disorders. We recruited the patients between 2016 and 2017 at Hyogo College of Medicine and Mihara Hospital, located in the central area of Osaka, Japan. All subjects voluntarily provided written informed consent to participate in this study. All of the patients with schizophrenia were diagnosed according to a Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria assessed by experienced psychiatrists (HY, MM, and HM). Patients with psychomotor excitation, impulsive or self-harm behaviors, suicide attempts, severe mental disability, and drug abuse were excluded from this study. The control group was defined by the absence of any history of psychiatric disorders as confirmed by screening with the questionnaire of the Structured Clinical Interview for DSM 4th edition, text revision (DSM-IV-TR). Participants with autoimmune diseases or inflammatory disorders were

Abbreviations: AGA, anti-gliadin; GS, gluten sensitivity; CD, celiac disease; GFD, gluten-free diet; CPZeq, chlorpromazine equivalents; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; SD, standard deviation; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression Scale-Severity of Illness; SOFAS, Social and Occupational Functioning Assessment Scale; CI, confidence interval; OR, odds ratio; TLR4, Toll-like-4 receptor; Th 17, T helper 17.

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excluded from this study. We confirmed that all participants did not have an unbalanced diet, restricted diet including GFD and abnormal eating habits. Eating habits of participants were basically similar.

All of the procedures in the current study complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the ethics committee at Hyogo College of Medicine (no. 2425). Detailed explanations of the study procedures were provided to each participant at the time we received their informed consent.

2.2. Study design

Each participant was screened for AGA-IgG and we divided all the participants into the two groups based on positive or negative for AGA-IgG. We analyzed the association between positive for AGA-IgG and negative for AGA-IgG of demographic and clinical features.

At the initial assessment, information was obtained in a face-to-face interview regarding each patient's demographic profile, medical history, clinical features, and course of illness. Specific parameters of all participants including age, sex, height, weight, educational level, employment status, presence or absence of food or drug allergies, medical history, a lifetime history of gastrointestinal symptoms and physical symptoms characteristic of GS (constipation, diarrhea, alternating bowel habits, abdominal pain, headache, foggy mind, and tiredness) were obtained. Regarding psychiatric assessments, clinical data were collected for each patient; such as onset of schizophrenia, history of medications, status of treatment (inpatient or outpatient), period of hospitalization, total number of hospitalizations, treatment resistance, duration and course of illness, and the results of psychiatric assessment scales. The daily dose of antipsychotic medication was determined from the medical records and converted into chlorpromazine equivalents (CPZeq). We classified the patients by daily CPZeq dose: < 600 mg/day or ≥ 600 mg/day. The definition of treatment resistant schizophrenia was confirmed with at least the minimum requirements provided by Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines [22]. Onset age was defined as the time when the clinical symptoms meeting DSM-5 diagnostic criteria for schizophrenia initially appeared. In terms of hospitalization, we labeled the patients who had been hospitalized longer than one year as "long-period" hospitalized patients. Furthermore, 4 psychometric properties were administered to each subject at the time of assessment: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale-Severity of Illness (CGI-S), DSM-IV-TR Axis 5 GAF and Social and Occupational Functioning Assessment Scale (SOFAS).

2.3. Blood measurements

Blood samples were obtained from all participants and centrifuged to collect the resulting supernatant, thus obtaining plasma. All plasma samples were frozen and stored at −30 °C until assayed. Plasma was analyzed for AGA-IgG antibody using ORG 534G kit (Orgentec Diagnostika, Mainz, Germany), which is a commercially available enzyme-linked immunosorbent assay (ELISA). All plasma samples were assayed using the kit described above in accordance with the manufacturer's protocol. The limit of detection of AGA-IgG was 0.5 U/ml. Positivity for AGA-IgG was determined by the manufacturer cutoff of AGA-IgG levels ≥12 U/ml. All samples were run in duplicate.

2.4. Statistical analysis

The sample size was calculated using G*Power3.1 and satisfied required the number of samples. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). We used Student's *t*-test or Welch's t-test to compare the averages of parametric variables with the calculation of 95% confidence interval (CI) and Pearson's chi-square test in cross tabulations to compare the proportions of categorical variables between the groups. The Mann-Whitney *U* test was used to compare changes between the groups in gluten sensitivity-related antibody values. Data were expressed as the mean and standard deviations (SDs) for continuous variables, and as frequencies and percentages for categorical variables. Logistic regression analysis was conducted to examine the factors affected by antibodies. All tests were two-tailed, and significance was defined as $P < 0.05$.

3. Results

3.1. Sample characteristics

The demographic profiles of the subjects are presented in Table 1. In this study, the final sample consisted of 110 participants: 60 patients in the schizophrenia group and 50 subjects in the control group. All participants were between 22 and 70 years old. There were no significant differences between the group of patients with schizophrenia and the control group in age, sex ratio, body mass index (BMI), or the percentage of presence or absence of any allergy history. At the time of the assessments, there were significant group differences in the duration of education, working status, and any gastrointestinal and physical symptoms such as constipation, diarrhea, foggy brain, and tiredness.

Within the patients with schizophrenia, the average (± SD) of onset age was 25.1 ± 7.8 years, duration of illness was 27.8 ± 14.2 years, duration of treatment was 26.6 ± 14.8 years, doses of antipsychotic (CPZeq doses) was 807.4 ± 593 mg/day, 32 (53%) were taking antipsychotics ≥600 mg/day (CPZeq doses), 35 (58%) were inpatients, the number of hospitalizations was 3.3 ± 2.9 and 28 (47%) were treatment-resistant cases. Twenty-nine (83%) of inpatients have been hospitalized for more than one year.

3.2. AGA-IgG in schizophrenia and controls

There were no significant differences in AGA-IgG positivity between the schizophrenia and control groups (18.3%; $n = 11$ *vs.* 12.0%; $n = 6$, $P = 0.433$). The plasma quantitative level of AGA-IgG is shown in Fig. 1. AGA-IgG plasma concentration was significantly higher in patients with schizophrenia than in control subjects (8.04 U/ml *vs.* 6.42 U/ml, $P = 0.05$).

Table 1
Demographic profiles and clinical features of the study groups.

	Schizophrenia ($n = 60$)	Healthy controls ($n = 50$)	*P*-value*
	Mean (range or SD) or *n* (%)		
Median age, years (range)	52.9 (22–70)	49.4 (31–67)	0.105
Sex, males	36 (60%)	21 (42%)	0.060
Body mass index (kg/m^2)	23.7 (5.2)	23.2 (4.1)	0.590
Education duration, years	11.3 (2.3)	15.9 (2.8)	< 0.001*
Employed	1 (1.7%)	50 (100%)	< 0.001*
Allergies	12 (20%)	8 (16%)	0.588
Gastrointestinal symptoms	28 (47%)	7 (14%)	< 0.001*
constipation	12 (20%)	3 (6%)	0.033*
diarrhea	10 (17%)	3 (6%)	0.084
alternating bowel habits	4 (7%)	0 (0%)	0.063
abdominal pain	2 (3%)	0 (0%)	0.193
Physical symptoms	27 (45%)	9 (18%)	0.003*
headache	11 (18%)	7 (14%)	0.541
foggy brain	12 (20%)	1 (2%)	0.004*
tiredness	10 (17%)	2 (4%)	0.034*

* *P* value is significant at the 0.05 level. SD; standard deviation.

3.3. Differences between AGA-IgG positive and negative groups in schizophrenia

We compared 11 patients with schizophrenia who were AGA-IgG positive with 49 patients who were AGA-IgG negative. Table 2 shows the results of comparisons of the demographic profiles and clinical features between patients with schizophrenia who were AGA-IgG positive and AGA-IgG negative. No significant differences in age, sex, BMI, education level, or history of allergic episodes were found between the groups. Patients who were positive to AGA-IgG tended to have a history of hospitalization compared with those who were negative to AGA-IgG (73%; $n = 8$ *vs.* 55%; $n = 27$, $P = 0.079$). The number of treatment-resistant patients with schizophrenia with positive AGA-IgG group was significantly higher than those with negative AGA-IgG group (82%; $n = 9$ *vs.* 39%; $n = 19$, $P = 0.017$). There were significantly more patients who received antipsychotics at doses >600 mg/day (CPZeq doses) in the positive AGA-IgG group than in the negative AGA-IgG group (82%; $n = 9$ *vs.* 47%; $n = 23$, $P = 0.048$). There were no significant differences in the severity of psychiatric symptoms, especially the PANSS score, including subscale scores between the groups. No significant group differences were detected in other clinical features such as age at onset, duration of illness or treatment, prevalence of longer-term hospitalizations, or of gastrointestinal and physical symptoms, number of hospitalizations, medication (multiple prescriptions of antipsychotics, anxiolytic or sleeping medications, mood stabilizers, and antiparkinsonian medications), CGI-S scores, GAF scores, or SOFAS scores.

Table 2
Comparison between anti-gliadin (AGA)-IgG positive and AGA-IgG negative in patients with schizophrenia.*

	AGA-IgG positive	AGA-IgG negative	*P*-value*
	($n = 11$)	($n = 49$)	
	Mean (SD) or *n* (%)		
Median age, years	50.7 (10.9)	53.4 (13.7)	0.547
Sex, males	6 (55%)	18 (37%)	0.321
Body mass index (kg/m^2)	23.0 (4.6)	23.9 (5.3)	0.618
Gastrointestinal symptoms	6 (55%)	23 (47%)	0.775
Physical symptoms	4 (36%)	23 (47%)	0.739
Antipsychotic dose, CPZeq (mg/day)	903.8 (594.4)	785.7 (597.4)	0.556
CPZeq ≥600 mg/day	9 (82%)	23 (47%)	0.048*
Inpatients / outpatients	18 (73%)/3 (27%)	27 (55%)/22 (45%)	0.079
Treatment resistance	9 (82%)	19 (39%)	0.017*
PANSS	70.1 (26.4)	67.0 (20.6)	0.667

CPZeq; chlorpromazine-equivalent daily dose, PANSS; Positive and Negative Syndrome Scale.
* *P* value is significant at the 0.05 level. SD; standard deviation.

3.4. AGA-IgG levels and clinical features in AGA-IgG positive schizophrenia

Plasma concentrations of AGA-IgG in AGA-IgG positive treatment-resistant patients with schizophrenia and AGA-IgG positive controls are shown in Fig. 2. We found that AGA-IgG concentration in AGA-IgG positive treatment-resistant patients was significantly higher than in AGA-IgG positive controls (26.3 U/ml *vs.* 21.3 U/ml, $P = 0.003$). Furthermore, we found that AGA-IgG concentration in treatment-resistant patients was significantly higher than that in non-treatment-resistant patients (10.79 U/ml *vs.* 5.19 U/ml, $P = 0.034$). The logistic regression analyses examined the relationship between plasma level of AGA-IgG and treatment-resistance in schizophrenia. The higher AGA-IgG plasma level was significantly associated with treatment resistance in patients

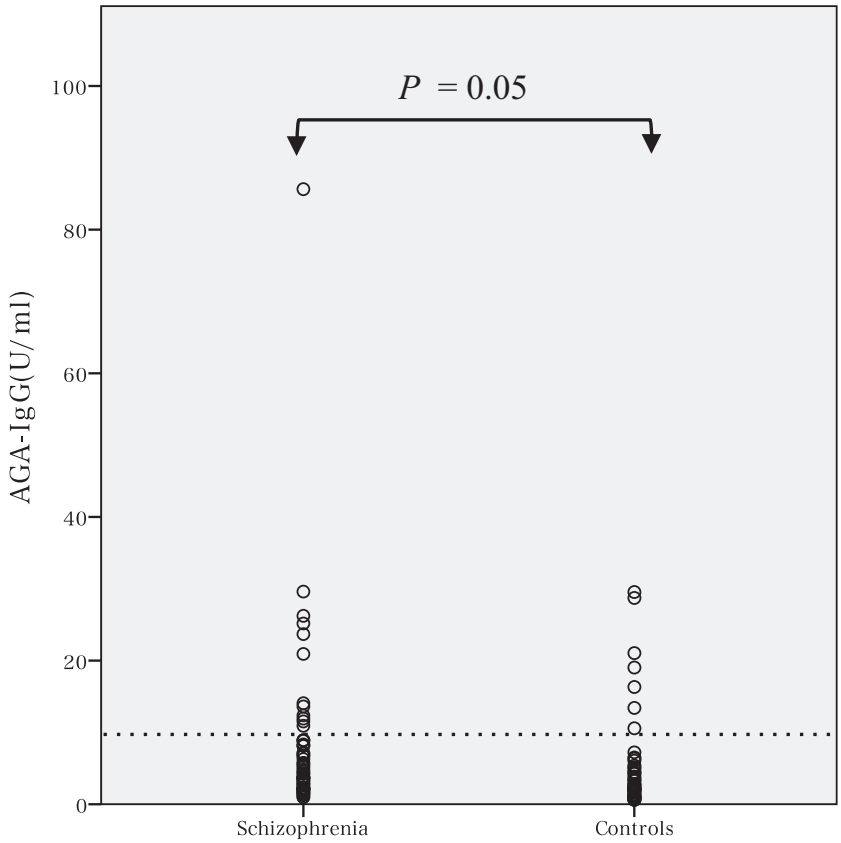

Fig. 1. Plasma quantitative level of AGA-IgG in patients with schizophrenia and healthy controls. AGA-IgG, anti-gliadin IgG.

with schizophrenia (odds ratio (OR) = 1.12, 95% CI = 1.01–1.23, P = 0.029).

Since one outlier case in treatment-resistant patients may have contributed to the elevated AGA-IgG in this group, we carried out statistical analysis without this outlier. Although no significant difference in AGA-IgG concentration was found between positive treatment-resistant patients and positive controls, AGA-IgG concentration in treatment-resistant patients was significantly higher than that in non-treatment-resistant (8.85 U/ml *vs.* 5.19 U/ml, P = 0.033). The higher AGA-IgG plasma level was significantly associated with treatment resistance in patients with schizophrenia in the logistic regression analyses (OR = 1.10, 95% CI = 1.00–1.21, P = 0.05) without this outlier.

4. Discussion

To our knowledge, this is the first study on the prevalence of immunological GS in schizophrenia and the clinical features in a Japanese cohort. In this study, we also investigated the relationship between clinical features associated with schizophrenia and immunological GS. Even though no significant difference was observed in AGA-IgG positivity between the groups of patients with schizophrenia and the control subjects, treatment-resistant schizophrenia was significantly more prevalent in the AGA-IgG positive group than in the AGA-IgG negative group. Furthermore, the number of patients with AGA-IgG positive schizophrenia who were taking antipsychotics ≥600 mg/day (CPZeq doses) was significantly higher than those with AGA-IgG negative. As for plasma levels of antibodies, the AGA-IgG plasma concentration was significantly higher in patients with schizophrenia than in controls. In addition, there was a significant relationship between high AGA-IgG plasma level and clinical variables related to treatment resistance. We conclude that immunological GS can be associated with schizophrenia and the response to antipsychotic drugs in schizophrenia, suggesting the existence of a subgroup of treatment-resistant patients with schizophrenia with elevated AGA-IgG.

Previous studies reported that the patients with schizophrenia had a three- to five-fold higher prevalence of AGA-IgG than the controls [7–9], which seems to be different from the results of our study. In our study, 12% of controls had AGA-IgG: an immunologic marker of GS. These findings suggest that GS may have a little higher prevalence in Japan than in Western countries. Further investigation is required to clarify this issue. Moreover, our small sample size was considered to be one of the factors in the difference with the findings of the previous study. An investigation with more samples is necessary.

Another study confirmed that the patients with recent-onset schizophrenia exhibited higher prevalence of AGA-IgG compared to controls. The patients with multi-episodic schizophrenia also tend to have a greater prevalence of AGA-IgG. In our study, we found that there were significantly more treatment-resistant patients with schizophrenia or the patients who currently required antipsychotics over 600 mg/day (CPZeq doses) in the group that was positive for AGA-IgG than the group that was AGA-IgG negative. This indicates that AGA-IgG may reflect a treatment response to antipsychotics in patients with schizophrenia. In general, GS is a syndrome characterized by colonic and extracolonic manifestations. Frequent colonic manifestations of GS are bloating, abdominal pain, epigastric pain, diarrhea and constipation; extracolonic manifestations involve lack of well-being, tiredness, headache, and foggy mind. GS is also associated with anxiety, depressed mood, mood swings, skin rash, and numbness, as well as other signs and symptoms [23]. Even though most symptoms of GS are similar to CD, GS refers to a wider range of physical and psychiatric symptoms compared to CD [24]. We therefore speculated that AGA-IgG could play an important role in the development of psychiatric symptoms or

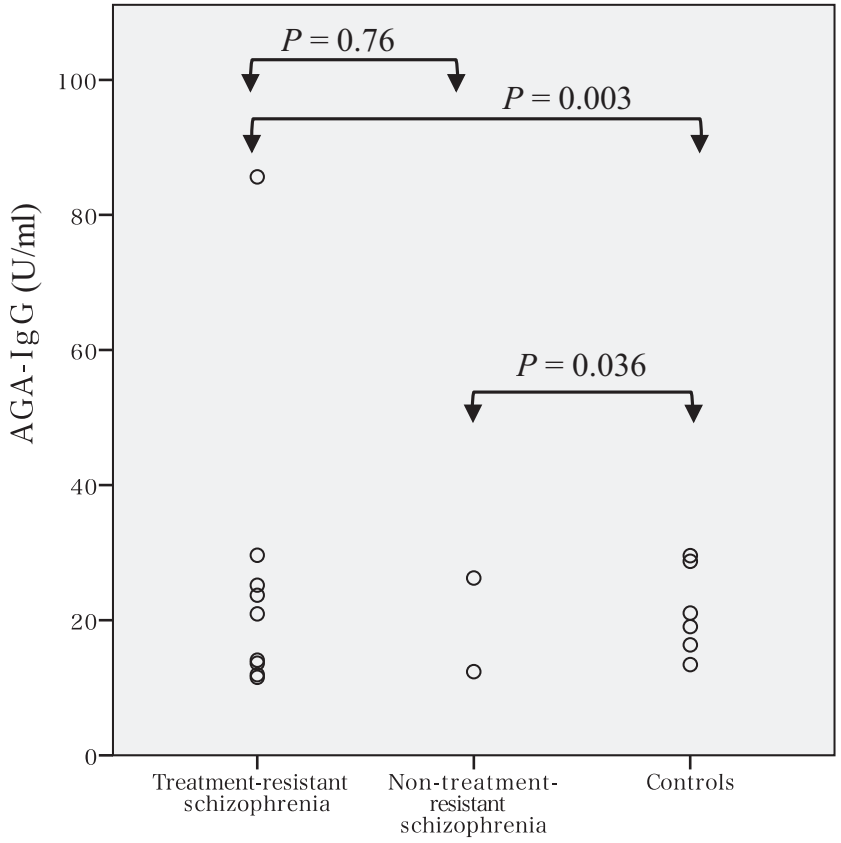

Fig. 2. Plasma quantitative level of AGA-IgG in treatment-resistant patients with AGA-IgG positive schizophrenia and controls. AGA-IgG, anti-gliadin IgG. Treatment-resistant schizophrenia, confirmed with at least the minimum requirements provided by Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines [33].

treatment response in patients with schizophrenia. Immunologic markers of GS may be biomarkers for identifying a specific subtype of schizophrenia and for predicting poorer treatment response.

Immunological mechanisms associated with GS may be involved with the highly expressed Toll-like-4 receptors (TLR4s), which play a crucial role in the innate immunity system in GS patients [25]. TLR4s are related not only to the activation of the innate immune system but also to the pathogenesis of autoimmune diseases. The association between schizophrenia and immunity has been known since the 1970s. It has been reported that a history of any autoimmune disease was associated with a nearly 50% increased risk for schizophrenia [26]. Indeed, several autoimmune diseases are more frequently observed among patients with schizophrenia than controls [27]. Other studies exploring the correlation between immune factors and schizophrenia have found that the T helper (Th) 17 cell-related cytokine levels were associated with positive, general and total PANSS scores, and the Th17 pathway is thought to play an important role in schizophrenia [28–30]. Th17 cells have a considerable effect on immune-regulatory activity, and the excessive activation of Th17 cells plays an important role in the onset of autoimmune and inflammatory diseases [31]. Th17 cells exist only in the gastrointestinal lamina propria mucosae. We have speculated that, in GS, lamina propria mucosae damaged by gluten could have changes in the activity of Th17 pathway.

The treatment for GS is gluten restriction. Several studies presented that the symptoms of schizophrenia were minimized with a GFD [32]. There is a case report of recovery from schizophrenia with GS by implementation of a GFD [33]. Thus, our next step is to investigate the therapeutic effects of a GFD on psychotic symptoms in schizophrenia patients with GS. If the effect is clearly confirmed, a new therapeutic approach for the patients with schizophrenia, especially with treatment-resistant schizophrenia, completely different from conventional pharmacotherapies, can be developed. The treatment intervention by a GFD is completely safe and convenient to apply. It needs future studies with a larger number of patients with schizophrenia to establish the clinical utility of GS as a biomarker for predicting treatment refractoriness in schizophrenia.

There are some crucial limitations to our study. First, our analyses had limited power to examine statistical significance because of the smaller sample size of each group. For instance, the finding that about half (47%) of our patients with schizophrenia were treatment resistant may be because of the small sample size along with possible sample bias. Furthermore, the bias may also be related to the recruitment of participants; 30 of 60 patients with schizophrenia were undergoing treatment at a psychiatric hospital (Mihara Hospital), where a higher proportion of treatment-resistant patients and patients with chronic schizophrenia are continuously treated. Among AGA-IgG positive people, the number of non-treatment resistant patients with schizophrenia was too small ($n = 2$) to examine statistical significance. Second, it was also difficult for us to evaluate the therapeutic effects of other interventions such as social skill training on the assessment of treatment refractoriness. Thus, to further examine the relationships among clinical features, treatment strategies and response, and GS, prospective follow-up studies are required. Third, as for gastrointestinal and physical symptoms, it was difficult for us to determine whether they were caused by gluten-related disease or side effects of antipsychotics, because of the lack of information regarding the temporal relationship between the development of gastrointestinal symptoms and the course of schizophrenia. Moreover, whether there is some causal effect of antipsychotics on the production of AGA-IgG remains unclear. A recent study suggested no significant association between antipsychotic medication and AGA-IgG levels, supporting the possibility that antipsychotics exert little effect on the production of AGA-IgG [34]. Prospective follow-up studies should be useful in clarifying these issues. Finally, there was one outlier case in the treatment-resistant patients. Although no significant difference in AGA-IgG concentration was found between positive treatment-resistant patients and positive controls without the outlier, the higher AGA-IgG plasma level was significantly associated with treatment resistance in patients with schizophrenia in the logistic regression analysis without it. Furthermore, we found that AGA-IgG concentration in treatment-resistant patients was significantly higher than that in non-treatment-resistant from the statistical analysis without it. The elevated AGA-IgG concentration appeared to be unaffected by the outlier.

5. Conclusion

In this study, we found no significant differences in the prevalence of immunological GS between the patients with schizophrenia and controls. Compared to the patients with schizophrenia without immunological GS, those with immunological GS showed more severe clinical features, such as a greater proportion of patients who required a higher dose of antipsychotics, and who were identified as refractory to treatment. Indeed, treatment-resistant patients or the patients who required antipsychotics ≥600 mg/day (CPZeq doses) were more frequently identified in AGA-IgG positive patients than in AGA-IgG negative patients. In addition, elevated AGA-IgG plasma level was associated with treatment resistance. Thus, the results of this study demonstrated the possibility of immunological GS being associated with poorer response to antipsychotics in schizophrenia. The possible utility of AGA-IgG as a biomarker for identifying the specific subtype of schizophrenia and for predicting outcome should also be examined in further studies, which may lead to the development of more personalized treatment for patients with schizophrenia.

Declaration of Competing Interest

All authors have read the journal's policy on disclosure of potential conflicts of interest and have none to declare.

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