International Journal of Medicine Research
ISSN: 2455-7404
www.medicinesjournal.com
Volume 3; Issue 1; January 2018; Page No. 23-27

A study of gluten sensitivity in patients suffering from schizophrenia

[1] Dr. Himanshu Singh, [*2] Dr. Vaibhav Dubey, [3] Dr. Mitali Loya, [4] Dr. Sanjeet Diwan, [5] Dr. Apurva Tiwari, [6] Dr. Sumera Khan
[1, 3, 4, 5, 6] MD Psychiatry, PCMS and RC-Bhopal, Madhya Pradesh, India
[2] MD Psychiatry, Associate Professor, PCMS and RC-Bhopal, Madhya Pradesh, India

Abstract
Background: In Asian countries about 70% patients suffering from schizophrenia are cared by their family members as compared to 25%-50% in western countries; this put an extra pressure of their routine and cost; early recognition can minimize this burden.
Aims and Objective: To study and correlate gluten sensitivity determined by the levels of anti-gliadin antibody (IgG) with duration and psychopathology in schizophrenia.
Materials and Methods: A cross-sectional study was performed on 30 schizophrenic patients fulfilling ICD-10 criteria in psychiatry ward of people's hospital, Bhopal from 2015-2017. Age, gender, total score on Brief Psychiatric Rating Scale version 4.0 (BPRS) and antigliadin antibody (AGA-IgG) titre (U/ml) were studied in all enrolled patients. Each psychotic symptom is rated 1-7 and a total of 24 symptoms are scored. All the data were analyzed using Statistical Package of Social Science Version 20; Chicago Inc., USA. Student t test, paired t test and chi square test were used to establish the level of significance. Significance was assessed at 5% level.
Results: Male preponderance was observed among Cases (63.3%) and controls (60%) (P=0.241). Patients having low AGA-IgG (<20) level were significantly high in Controls (n=21) compared to Cases (n=4) (p<0.001) whereas there were significantly more number of patients in Cases (n=17) who had high (>30) AGA-IgG levels compared to Controls (n=1) (p=0.002). BPRS score (r=0.231, p=0.089) and duration of illness (r=0.213, p=0.078) have shown positively correlation with the AGA-IgG values. No significant difference was obtained while comparing AGA-IgG values between gender (p=0.705).
Conclusion: Immune pathological abnormalities associated with raised antibodies are present in the course of the disease and may worsen with the disease progression. Hence screening of patients with schizophrenia by laboratory test for Gluten sensitivity can be performed routinely.

Keywords: gluten sensitivity, BPRS score, schizophrenia, antigliadin antibody, ICD-10 criteria

Introduction

Schizophrenia is a chronic illness that characteristically has its onset in young age and lasts a lifetime with only occasional recovery in few patients [1, 2]. The characteristic features of the disorder are hallucinations, delusions, disorganized speech, disorganized behavior, paranoia, thought disorder as well as negative symptoms [3, 4].

Schizophrenia is an incapacitating psychiatric disorder that affects 3-6.6 persons per 1000 population [5]. According to the World Health Organization (WHO) estimate in year 2016, there are more than 21milion people suffering from schizophrenia worldwide [6]. It is ranked 8th leading cause of disability adjusted life years in the age group of 15 to 44 years. The estimated direct costs of schizophrenia in western countries range from 1.6% to 2.6% of the total healthcare expenditure [7].

The nature of illness has posed a significant burden to the patients as well as family members. In Asian countries about 70% patients suffering from schizophrenia are cared by their family members as compared to 25%-50% in western countries [8]. This leads to enormous burden for the family members in terms of financial, social, physical and mental health [9].

In recent times, Gluten sensitivity (GS) has emerged as a distinct clinical entity [10], also called Non Celiac Gluten sensitivity (NCGS). It was first described in 1980 [11] and is characterized by mainly extra-intestinal symptomssuch as behavioral changes, numbness in legs, muscle cramps, bone and joint pain, weight loss and fatigue. It is related to the consumption of gluten-containing food, in people that are not affected with either celiac disease (CD) or wheat allergy (WA) [11]. Antibodies which are generally found in CD (transglutaminase, antiendomysin) are usually not detected in GS but rather they can test positive for antibodies to gliadin. Interleukin 17A found in patients with CD is also absent in the patients of GS [10]. There is a genetic association with the major histocompatibility complex (MHC) class II haplotypes in CD patients, 95% of CD patients have HLA-DQ2 and only 5% have HLA-DQ8 but only 50%of GS patients appear positive for this genetic make-up [12].

The importance of Gluten Sensitivity in schizophrenia was suggested by Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study where it was concluded that the age-adjusted prevalence (23.4%) of anti-gliadin antibodies in people with schizophrenia (N = 1473) was significantly higher than that observed in general population [13] It was further supported in a similar study which concluded that patients with schizophrenia with recent onset of symptoms had increased levels of IgA and IgG antibodies to gliadin compared to both controls and schizophrenics with multi-

episodes. [14]

Hence, Present study was performed to study and correlate gluten sensitivity determined by the levels of anti-gliadin antibody (IgG) with duration and psychopathology in schizophrenia.

Materials and Methods

Present cross-sectional case control study was done in psychiatry ward of peoples hospital on 30 patients suffering from schizophrenia comprising of 19 male and 11 female patients fulfilling ICD-10 [15] criteria for the diagnosis and compared with 30 normal healthy controls comprising of 18 males and 12 females.

Study variables including age, gender, total score on Brief Psychiatric Rating Scale version 4.0 (BPRS) [16], and antigliadin antibody (AGA-IgG) titre (U/ml) were studied.

Cases of schizophrenia identified by ICD 10 [15] diagnostic criteria and having age between 18- 45 years were included whereas patients having psychosis other than schizophrenia, age below 18 and above 45 and patients unwilling to participate were excluded from the present study.

After a complete description of the study to enrolled patients; written informed consent was obtained from all and Ethics committee approval was obtained from the Institutional Ethical Committee. Illness-related variables were rated with the BPRS at the time of first encounter. This was a one point, comparative study where we compared Antigliadin antibody-IgG levels in schizophrenia patients and healthy controls. All patients fulfilling the inclusion criteria and who have given the written consent were then interviewed. Apparatus and materials

Psychotic symptoms were objectively measured by BPRS, antigliadin antibody (IgG) was measured using ELISA test and physical and mental examination was carried out thoroughly.

Data collection

All cases of schizophrenia were examined in detail clinically and their mental status was assessed. Psychopathology was objectively measured by BPRS version 4.

2ml of blood was collected under strict aseptic conditions. Collected whole blood was allowed to clot for 30 minutes at room temperature. Serum was separated from clot by centrifugation. Obtained serum samples were labelled alpha numerically and stores at -70ºC. Human Antigliadin IgG was measured as per the guidelines of the originators. Same procedure was followed to obtain blood sample of subjects in control group.

Brief psychiatric Rating scale (BPRS) Version 4.0: This is a modified version with 24 items. It is the most widely used instrument in psychotic conditions. The total scores are highly correlated with total scores of PANSS. The items of this instrument give ample opportunity to assess all aspects of phenomenology of schizophrenia.

Each symptom is rated 1-7 and a total of 24 symptoms are scored. The symptoms are somatic concern, anxiety, depression, suicidality, guilt, hostility, elated mood, grandiosity, suspiciousness, hallucinations, unusual thought content, bizarre behavior, self-neglect, disorientation, conceptual disorganization, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity and mannerisms and posturing.

All the data were analyzed using Statistical Package of Social Science (SPSS Version 20; Chicago Inc., USA). Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Quantitative variables were compared using mean values and qualitative variables using proportions. Significance level was fixed at $P < 0.05$.

Result

In present study, most of the subjects among Cases (36.66%) and Controls (36.66%) belong to age group of 31-40 years (P=0.142). Male preponderance was observed among Cases (63.3%) and controls (60%) (P=0.241).

Most of the subject among Cases (70%) and Controls (76.7%) belong to Urban population (P=0.116). Among Cases and Control, most of the subjects had postgraduate (36.7%) and intermediate education (43.3%) respectively (P=0.067).

Out of 30 ases, most of them were unskilled (66.7%), 33.3% were semiskilled none of them were skilled whereas out of 30 controls, most of them were semiskilled (46.7%), 36.7% were skilled and 16.7% were unskilled (P=0.012).

Table 1: Comparing values of AGA-IgG between cases and Controls

AGA-IgG group	Cases	Controls	Chi square value	df	P value
Low (<20)	4 (13.33)	21 (70)	20.600	2	<0.001
Medium (20-30)	9 (30)	8 (26.67)	8.764	2	0.874
High (>30)	17 (56.33)	1 (3.33)	24.620	2	0.002

Data is expressed as no of patients (%), AGA-IgG); antigliadin antibody, df; degree of freedom

Table 2: Showing Correlation between BPRS score and Duration of illness with AGA-IgG values of cases

Parameter		AGA-IgG VALUEP
BPRS Score P	Pearson Correlation	0.231**
	Sig. (2-tailed)	.089
	N	30
Duration of illness	Pearson Correlation	0.213**
	Sig. (2-tailed)	0.078
	N	30

**Correlation is significant at the 0.01 level (2-tailed). Data is expressed as no of patients (%), AGA-IgG); antigliadin antibody, df; degree of freedom, N; no of patients

The mean BPRS, AGA-IgG value and score of duration of illness of the cases was 51.37±10.377, 28.87±8.253 and

11.2000±6.672 respectively. While comparing AGA-IgG values between gender, no significant difference was obtained (p=.705).

Discussion

Several studies have observed that some schizophrenia patients have elevated levels of anti-gliadin antibodies [14, 17]. Schizophrenia has been linked to anti gliadin antibodies and celiac disease in several studies [13, 18]. This has been proven in various studies that patients suffering from schizophrenia when put on a gluten free diet, reported improvement in symptoms as well as BPRS score and recurrence of symptoms when gluten was added in the diet [19, 21]. Lionetti *et al* [20] suggested that neuropsychiatric symptoms in the patients of gluten sensitivity may be due to leaky gut which may lead the gluten peptides to cross the intestinal membrane and blood brain barrier and finally affect the endogenous opiate system and neurotransmitter or gluten peptides may activate innate immune response in brain leading to symptoms of schizophrenia.

In the case group we considered patients who were either drug naïve or who did not take treatment for more than six months. We did not find any study relating the role of neuroleptics, affecting the level of anti-gliadin antibodies. Though several studies conducted in the past did not consider this criterion, we did so to prevent any bias if so occurs. We assumed that both the case and control group would have consumed wheat containing products in nearly equivalent amounts.

Various studies have been conducted in the past to assess the association of specific classes of antibodies with schizophrenia, but the results have been inconsistent. Dickerson *et al* [14] reported increased level of AGA-IgG in patients of schizophrenia while Jin *et al* [22] and Cascella *et al* [13] found AGA-IgA antibodies to be significantly elevated in schizophrenia but not AGA-IgG. This inconsistency in the findings related to AGA-IgG antibodies could be due to relatively small sample size in the previous studies or might be due to geographical location and thus the staple diet of the study population. Ours is a tropical country with staple diet of study population being wheat, we wanted to study the association of gluten sensitivity by studying the level of AGA-IgG in the cases and controls.

In present study we found that the mean anti-gliadin antibody-IgG value in cases were higher (28.87±8.253U/ml) as compared to the controls (15.17±7.149U/ml) (p<0.001). Similar finding has been previously documented by Jackson *et al* (Jackson J 2014) and Dickerson *et al* [14] where they also found the increased mean values of AGA-IgG in patients of schizophrenia as compared to healthy controls. These studies also evaluated the levels of other antibodies including Anti-Gliadin antibody -IgA, antibody to deamidated gliadin, IgG and IgA antibodies to tTg, to rule out Celiac disease in the patients suffering from schizophrenia and in the healthy controls. Cade *et al* (Cade R 2016) found the increased frequency of AGA-IgG antibodies in patients of schizophrenia and autism as compared to normal volunteers. Samaroo *et al* [17] in their study compared the levels of Anti-Gliadin antibody-IgA along with Anti-Gliadin antibody-IgG between patients of Schizophrenia and celiac disease, found that levels of anti-gliadin antibodies were lower in patients of Schizophrenia as compared to patients of celiac disease. In our study we did not compare the values of these antibodies due to financial constraints.

Based on Cascella *et al* [13], we divided the cases and the controls who had AGA-IgG in a range of 20-30U/ml. We measured AGA-IgG as a dichotomous measure i.e., >30 vs <20. We found that the patients having low AGA-IgG (<20) level were significantly high in the Control (n=21) group as compared to the Cases (n=4) (p<0.001) whereas there were significantly more number of patients in the Cases (n=17) who had high (>30) AGA-IgG levels compared to the Controls (n=1) (p=0.002). These results suggest that AGA-IgG antibodies are significantly higher in the patients of schizophrenia as compared to the controls. This also suggests the possible immune etiology and the role of gliadin in the pathophysiology of schizophrenia. The results of our study are affirmed by studies conducted in the past which concluded higher Anti-Gliadin antibody in the patients of schizophrenia as compared to the healthy controls [13, 22].

BPRS score of the cases was positively correlated with the AGA-IgG values i.e. as the BPRS score of the patients increased the AGA-IgG values also increased. But the Pearson correlation revealed no significant difference between the two values (p=0.089). Cade *et al* [23] compared the BPRS score of the patients of schizophrenia when put on dialysis and on gluten free diet and concluded that BPRS score reached a normal value and patient regained normal functioning in their life after dialysis or gluten free diet (GFD). Jackson *et al* [24] compared the BPRS score between AGA positive and AGA negative schizophrenia group and did not find much difference between the two groups in the BPRS score except a minor decrease in three item BPRS positive symptom score(sum of items for hallucinations, delusions and conceptual disorganization) in the AGA positive patients of schizophrenia. Jackson *et al* [21] reported improvement in BPRS score, when patients who were positive for either anti-tTG or AGA were put on a gluten free diet. Rice *et al* [25] also reported regression in BPRS score below baseline when patients were put on a gluten free diet. This suggests that the clinical presentation of schizophrenia might be dependent on gliadins. Insignificant results in present study may be due to sample size.

Although the duration of illness was positively correlated with the AGA-IgG values, (which means as the duration of illness increases, AGA-the IgG values also increases) but was not significant (P= 0.078). We did not find any study, which compared the above two parameters but Dickerson *et al* [14] in their study reported that patients with Recent onset Psychosis (n=129, mean=2.17±1.77) had higher values of AGA-IgG as compared to patients with Multi-Episode Schizophrenia (n=191, mean=1.40±1.03) and non-psychiatric controls (n=151,mean=1.0±.61) (p=<.0001).

We also compared the values of AGA-IgG between gender in the cases to find out whether gender of the person is related to difference in the values of AGA-IgG. We did not find significant difference between the values of AGA-IgG when we compared them between the two genders, hence the results of our study suggest that the gender does not affect AGA-IgG values. Jin *et al* [22] studied the effect of gender leading to a difference in the levels of AGA-IgA values in the cases and

controls and found that female population in control group had low level of AGA-IgA, leading to significant difference between two groups. Though their study did not show significant difference when they compared the levels of AGA-IgG antibodies between cases and control group. They further compared the prevalence of AGA-IgA between female and male patients as compared to control group and found that the prevalence of AGA-IgA was significantly higher in female patients and marginally higher in male patients than control group. Cascella *et al* [13] in the CATIE study also pointed out the gender difference between female and male patients and concluded that AGA-IgA level was slightly higher in female patients than male patients but it was statistically insignificant. Jin *et al* [22] possibly explained the gender difference in the level of gliadin antibody, reflects etiological heterogeneity leading to clinical heterogeneity of the illness. They correlated this to be the possible reason for the difference in clinical presentation in female and male patients suffering from schizophrenia. Female patients suffering from schizophrenia present with late onset, lesser level of disability, better premorbid functioning, more positive and affective symptoms [26], whereas male patients presented with early age of onset, profound negative symptoms, lesser premorbid functioning, differential neuron cognitive functioning, poor response to antipsychotic medication and reduced emotional perception [27]. The difference in the gender might be true for AGA-IgA as reported by the aforementioned studies, but not for AGA-IgG. The absence of difference in the level of AGA-IgG between genders in cases could be due to small sample size of our study or due to ethnic/racial factors. Further studies are needed in future to ascertain AGA-IgG variation with genders. Present study have few limitation as we did not compare the values of other antibodies like AGA-IgA, antibody to deaminated gliadin, IgG and IgA antibodies to tTG, to rule out Celiac disease in the patients suffering from Schizophrenia and in the healthy controls due to financial constraints. We did not put the cases on gluten free diet or dialysis to see the effect on the symptoms and the sample size of our study population was small therefore a large randomized clinical trial is needed to strengthen the present study findings.

Conclusion

We conclude that increased levels of AGA-IgG antibodies in the patients of schizophrenia suggest that the immune pathological abnormalities associated with raised antibodies are present in the course of the disease and may worsen with the disease progression. Symptom profile will not distinguish the people with schizophrenia who have gluten sensitivity from the people with schizophrenia who do not have gluten sensitivity, so screening of patients with schizophrenia by laboratory test for gluten sensitivity can be performed routinely.

References

1. Carpenter WT Jr, Buchanan RW. Schizophrenia review. N Engl J Med. 1994; 330:681-690.
2. Tamminga CA, Thaker GK, Medoff DR. Neuropsychiatric Aspects of Schizophrenia. Textbook of Neuro psychopharmacology. 4th ed; Washington, DC: American Psychiatric Press, 2001.
3. Andreasen NC. Symptoms, signs, and diagnosis of schizophrenia review. Lancet, 1995; 346:477-481.
4. Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. Br J Psychiatry, 1987; 151:145-151.
5. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic reviews. 2008; 30(1):67-76. pmid:18480098,
6. World Health Organization. Schizophrenia. Retrieved on 2016-2010.
7. Barbato A. Schizophrenia and Public Health. Geneva: World Health Organization, 1998.
8. Chan SW. Global perspective of burden of family caregivers for persons with schizophrenia. Archives of psychiatric nursing. 2011; 25(5):339-49, pmid:21978802,
9. Harvey K, Catty J, Langman A, Winfield H, Clement S, Burns E, *et al*. A review of instruments developed to measure outcomes for carers of people with mental health problems. Acta psychiatrica Scandinavica. pmid:182 41311, 2008; 117(3):164-76.
10. Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Cartenì M, Casolaro V, Fasano A, *et al*. Differential mucosal IL-17 expression in two gliadin-induced disorders: Gluten sensitivity and the autoimmune enteropathy celiac disease. Int. Arch. Allergy Immunol, 2010; 152:75-80.
11. Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. Gastroenterology, 1981; 81:192-194.
12. Bizzaro N, Tozzoli R, Villalta D, Fabris M, Tonutti E. Cutting-edge issues in celiac disease and in gluten intolerance. Clinical Reviews in Allergy and Immunology, 2010.
13. Cascella NG, Kryszak D, Bhatti B, Gregory P, Kelly DL, Mc Evoy JP, *et al*. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. Schizophrenia Research, 2011; 37:94-100.
14. Dickerson F, Cassie Stallings, Andrea Origoni, Crystal Vaughan, Sunil Khushalani, *et al*. Markers of Gluten Sensitivity and Celiac Disease in Recent-Onset Psychosis and Multi-Episode Schizophrenia; BIOL PSYCHIATRY 2010; 68:100-104.
15. World Health Organization. The ICD-10 classification of mental and behavioral disorders. World Health Organization: Geneva, 1992.
16. Leucht S, Kane JM, Kissling W, *et al*. Clinical Implications of BPRS. Brit J of psychiatry, 2005; 187:366-371.
17. Samaroo D, Dickerson F, Kasarda DD, Green PH, Briani C, Yolken RH, *et al*. Novel immune response to gluten in individuals with schizophrenia. Schizophrenia Research, 2010; 118:248-255.
18. Bender L. Childhood schizophrenia. Psychiatric Quarterly, 1953; 27:663-681.
19. De Santis A, Addolorato G, Romito A, Caputo S, Giordano A, Gambassi G, *et al*. Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: Regression

after a gluten-free diet. Journal of Internal Medicine, 1997; 242:421-423.
20. Lionetti E, Salvatore Leonardi, Chiara Franzonello, Margherita Mancardi, Martino Ruggieri, Carlo Catassi; Gluten Psychosis: Confirmation of a New Clinical Entity; Nutrients, 2015; 7:5532-5539.
21. Jackson JR. William W, Eaton Nicola G, Cascella Alessio Fasano, Deanna L. Kelly. Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity. Psychiatr Q, 2012; 83:91-102.
22. Jin SZ, Wu N, Xu Q, Zhang X, Ju GZ, Law MH, *et al*. A study of circulating gliadin antibodies in schizophrenia among a Chinese population. Schizophrenia Bulletin, 2012.
23. Cade R *et al*. Autism and Schizophrenia: Intestinal Disorders, nutritional neuroscience, 2016.
24. Jackson J, William Eaton, Nicola Cascella *et al*. Gluten sensitivity and relationship to psychiatric symptoms in people with schizophreniaSchizophr Res. 2014; 159(0):539-542.
25. Rice JR, Ham CH, Gore WE. Another look at gluten in schizophrenia. American Journal of Psychiatry, 1978; 135:1417-1418.
26. Tang YL, Gillespie CF, Epstein MP, *et al*. Gender differences in 542 Chinese inpatients with schizophrenia. Schizophr Res. 2007; 97:88-96.
27. Chaves AC, Seeman MV. Sex selection bias in schizophrenia antipsychotic trials. J Clin Psychopharmacol. 2006; 26:489-494.