Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2020 Jul-Aug;42(4):398-402
doi:10.1590/1516-4446-2019-0699
Brazilian Psychiatric Association

ORIGINAL ARTICLE

Serum galectin-3 levels are decreased in schizophrenia

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Objective: To determine whether changes in serum galectin-3 (gal-3) concentrations in schizophrenia patients have etiopathogenetic importance. Since very little research has assessed the connection between galectins and schizophrenia, we wanted to examine alterations in the inflammatory marker gal-3 in schizophrenia and investigate possible correlations between clinical symptomatology and serum concentrations.
Methods: Forty-eight schizophrenia patients and 44 healthy controls were included in this study. The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were administered to determine symptom severity. Venous blood samples were collected, and serum gal-3 levels were measured.
Results: Mean serum gal-3 levels were significantly lower in schizophrenia patients, and there were no significant differences in age or sex with the control group. There was also a significant positive correlation between serum gal-3 concentrations and negative schizophrenia symptoms according to the SANS.
Conclusion: The results indicate that gal-3 is decreased in schizophrenia patients, which could contribute to inflammation in the pathogenesis of schizophrenia.

Keywords: Schizophrenia; galectin-3; serum level; neuroinflammation

Introduction

Schizophrenia is a chronic, debilitating mental disorder, affecting roughly 1% of the world population and characterized by distortion of thought, language, emotion, perception, and behavior.[1,2] Schizophrenia's fundamental mechanisms have been gradually revealed through technological innovations in neuroimaging, genetics, and neurobiology, but its etiopathogenesis is still obscure. The research and identification of biomarkers of schizophrenia is an especially active field of psychiatric studies.

In the last few years, substantial clinical and molecular research has attempted to determine the role of immune impairment in schizophrenia and has investigated targeting these pathways as an add-on to current therapies.[3,4] Numerous studies have discovered that the blood levels of inflammatory cytokines have increased in individuals with schizophrenia.[5] Several proteins have been researched as potential biomarkers to elucidate the significance of inflammation in mental disorders.

Galectins are a family of 15 glycan-binding proteins, and increasing evidence indicates that galectins can behave as an endogenous modulator for inflammatory reaction and potential neurodegenerative effects.[6,7] Galectin-3 (gal-3), a unique member of this family, has also been the most researched.[8] Gal-3 impacts sensitivity to autoimmune and inflammatory diseases mediated by T-cells.[9] Increased soluble and/or cellular gal-3 concentrations have been correlated with autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Behcet disease.[10] Gal-3 is discovered in different kinds of cells and tissues and its distinct functions have been outlined, including promoting cell migration, stimulating proliferation, survival, differentiation, adherence, apoptosis, and immune response.[11] Experimental studies have shown that upregulation of gal-3 gene expression occurs after neuronal injury, such as traumatic spinal cord injury and experimental autoimmune encephalomyelitis.[12-14] In addition, gal-3 deficient mice, especially regarding the hippocampus and striatum, have been found to be preserved against ischemic injury.[12] Studies have shown that gal-3 contributes to certain neurological conditions, such as Parkinson disease,[15] prion diseases,[16] and amyotrophic lateral sclerosis.[17] In addition to these studies, gal-3 has also been researched in relation to psychiatric disorders, such as attention deficit hyperactivity disorder,[18] schizophrenia[19,20] and anxiety.[21] To the best of our knowledge, very few studies have evaluated the connection between galectins and schizophrenia.

In this context, we wanted to examine alterations in the inflammatory marker gal-3 in schizophrenia and investigate

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Submitted Sep 08 2019, accepted Nov 12 2019, Epub Mar 09 2020.

How to cite this article: Kılıç F, Işık U, Demirdaş A, Usta A. Serum galectin-3 levels are decreased in schizophrenia. Braz J Psychiatry. 2020;42:398-402. http://dx.doi.org/10.1590/1516-4446-2019-0699

possible correlations between clinical symptomatology and serum concentrations.

Methods

Subjects

The sample consisted of 48 patients (13 women and 35 men) diagnosed with schizophrenia in accordance with the DSM-IV at the Department of Psychiatry, S. Demirel University School of Medicine, Isparta, Turkey. A DSM-IV schizophrenia diagnosis was established on the basis of one senior psychiatrist's ongoing clinical interviews. Patients with any axis I psychiatric disorder were excluded. There is notable heterogeneity in the existing studies of inflammatory cytokines in schizophrenia. For example, studies have used patients at different stages of the disorder,[22] i.e., they selected patients who did not suffer from acute psychotic episodes. The patients included in this study had been using antipsychotic drugs regularly for the last year and had used no other medications besides psychotropic drugs. The control group consisted of 44 healthy hospital staff members, matched by age and gender, who had no history of mental disorders and were not on any medications. The participants' demographic and clinical features were acquired through interviews (all respondents) and medical records (patients). None of the respondents had a history of serious physical illness, including cardiac illness, chronic renal illness, cancer, neurological disorders, chronic infections, or immunological illnesses.

Clinical assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate schizophrenia symptoms. Andreasen developed the SAPS to assess the level, distribution and severity of change in positive schizophrenia symptoms.[23] Erkoç et al. studied the validity-reliability of the Turkish version.[24] Andreasen developed the SANS to assess the level, distribution and severity of change in negative schizophrenia symptoms.[23] Erkoç et al. studied the validity-reliability of the Turkish version.[25]

Determination of serum galectin-3 levels

Venous blood specimens from the left forearm vein were gathered into heparinized tubes between 08.00 and 09.00 hours after overnight fasting. To remove plasma, the blood samples were centrifuged at 3,000 rpm at 4 °C for 10 minutes. Until analysis, the serum specimens were stored at -80 °C. A commercial ELISA kit [Human GAL3 (Galectin 3); Catalog No: E-EL-H1470; Elabscience Biotechnology Inc.] was used to measure gal-3 serum concentrations according to manufacturer instructions. Serum gal-3 levels were recorded in ng/mL.

Statistical analysis

Our data were analyzed in SPSS version 18. The Kolmogorov-Smirnov test was used to determine normal distribution of the variables. The data were shown as a mean and standard deviation and evaluated using descriptive analysis. Relationships between categorical data were evaluated with the chi-square test. The psychological outcomes and biochemical parameters of the patient and control groups were compared with Student's *t*-test or the Mann-Whitney *U* test. To analyze the correlations between clinical features and serum gal-3 levels, the Spearman rank correlation coefficient was used. Galectin-3 levels were log-transformed and used in analysis of covariance (ANCOVA) to compare group mean differences using age and sex as covariate factors. P-values < 0.05 (two-tailed) were considered significant.

Ethics statement

After a full description of the study, all participants gave written informed consent according to the Helsinki Declaration. The study was approved by the local ethics committee.

Results

This study included a total of 48 patients (13 women and 35 men) with an average age of 37.7±10.5 years (range 19-55). The control group (n=44) included 15 women and 29 men with a mean age of 38.2±7.1 years (range 25-56). There were no significant differences between patients and controls regarding age, sex, or smoking status, but there were significant differences in body mass index (BMI) (29.7±6.0 in patients and 25.5±3.6 in controls) ($p < 0.001$). Table 1 summarizes the demographic characteristics of all participants and the clinical information of the patient group. The mean age at schizophrenia onset was 23.7±8.5 years and the mean illness duration was 14±9.4 years. The mean SANS and SAPS scores in the patient group were 49±28 and 22.6±23.7, respectively. The patients' drug regimens were as follows: single antipsychotic (n=19), multiple antipsychotics (n=18), or oral form and depot formulation of atypical antipsychotics (n=11). The mean duration of medication use was 13.2±9.3 years. Fourteen patients had attempted suicide.

The mean serum gal-3 levels were 2.25±1.33 ng/mL in patients and 2.74±1.25 ng/mL in controls ($z = -2.232$, $p = 0.026$). The significant difference in gal-3 levels was maintained in ANCOVA, even after controlling for age and sex ($F = 7.323$, $\eta_p^2 = 0.77$, $p = 0.008$) (Table 1 and Figure 1). In addition, correlations were examined between serum gal-3 concentrations and age, BMI, disease onset, disease duration, and clinical variables such as SAPS and SANS scores (Table 2). Although there was no significant correlation between serum gal-3 concentration and total SAPS score, there was a significant positive correlation between serum gal-3 concentration and SANS score ($r = 0.335$; $p = 0.020$).

Table 1 Demographic and clinical characteristics of schizophrenia patients and controls

	Schizophrenia (n=48)	Controls (n=44)	*t*/z/chi-square	p-value
Age (years)	37.7±10.5	38.2±7.1	-0.242*	0.809
Sex				
Male/Female	35/13	29/15	0.532†	0.466
Smoking				
Smoker/nonsmoker	30/18	19/25	3.442†	0.064
BMI	29.7±6.0	25.5±3.6	-3.760‡	< **0.001**
Galectin-3 (ng/mL)§	2.25±1.33	2.74±1.25	-2.232‡	**0.026**
History of suicide attempt				
Yes/no	14/34			
Duration of illness (years)	14±9.4 (1-37)			
Duration of antipsychotic use (years)	13.2±9.3 (0-36)			
SAPS	22.6±23.7			
SANS	49±28			

BMI = body mass index; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms. Bold type denotes statistical significance.
* Student's *t*-test; † chi-square test; ‡ Mann-whitney *U* test.
§ Log-transformed variables; analysis of covariance was used after adjustment for age and sex for comparisons between the groups: $F_{1,88}$ = 7.323, p = 0.008, η_p^2 = 0.77.

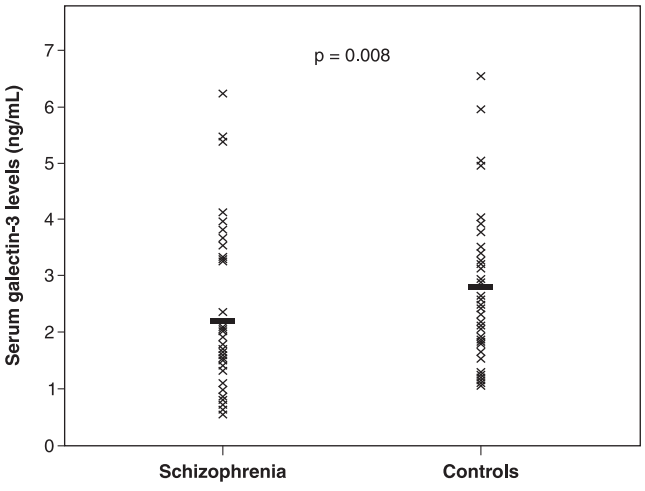

Figure 1 Dot plots representing the distribution of serum Galectin-3 levels in schizophrenia patients and controls. After adjusting for age and sex, analysis of covariance was used for comparisons between the groups.

Discussion

While the underlying mechanisms in the pathogenesis of schizophrenia are still unknown, experimental information from patient serum and cells are providing clues about the answer. Gal-3 is a multifunctional protein that involves fibrosis, neurogenesis, apoptosis, and immune activation[11] in a number of biological processes, some of which are connected with the development of schizophrenia.[26] As an early step toward resolving this issue, we evaluated serum gal-3 concentrations and their associations with the clinical features of schizophrenia. The main results of our study are that there is a significant decrease in serum gal-3 levels in schizophrenia patients. In addition, an important positive correlation was found between SANS scores and serum gal-3 levels.

It has been reported that gal-3 has functional roles in the central nervous system (CNS).[14] Gal-3 induction has been reported in several brain pathologies, including prion disease, amyotrophic lateral sclerosis, Alzheimer's disease, and ischemic brain lesions.[16,17,27,28] Gal-3 has also been studied in psychiatric disorders. To our knowledge, this is only the third investigation into gal-3 levels in schizophrenia patients. Borovcanin et al. showed that serum concentrations of gal-3 were significantly lower in first-episode psychosis and schizophrenia in relapse than in healthy controls.[20] They also found higher gal-3 levels in schizophrenia in remission. The authors suggested that gal-3 may mediate the underlying mechanisms of schizophrenia onset, as well as metabolic and cardiovascular changes in these patients. Kajitani et al. found that serum gal-3 levels were elevated in schizophrenia patients,[19] unlike our results. In another study, Stajic et al. studied behavioral changes in mice after gal-3 gene deletion,[21] finding that gal-3 gene deletion prevented IL-6 increases and led to a decline in brain-derived neurotrophic factor gene expression and immunoreactivity, as well as a reduction in hippocampal GABA-AR2S, thus attenuating the anxiogenic effect of neuroinflammation.[21]

In recent years, there has been an increasing number of studies on the relationship between inflammatory cytokines and schizophrenia. High concentrations of inflammatory mediators have recently been recorded in the serum of schizophrenia patients, such as IL-1β, IL-6, and TNF-α,[5] and neuroinflammation may contribute to the pathogenesis of schizophrenia.[29] Many cytokine receptors are located in the CNS.[30] The presence of cytokine receptors on neurons indicates that cytokine directly affects the activity of the neuron.[31] Borovcanin et al. found that, compared to healthy controls, serum levels of IL-4 and TGF-β were increased and serum concentration

Table 2 Correlation between galectin-3 levels and various clinical parameters

Galectin-3	Age of onset	Duration of illness	Duration of antipsychotic use	BMI	SANS	SAPS
r	-0.279	-0.153	-0.222	-0.065	**0.335***	0.067
p	0.055	0.300	0.130	0.662	**0.020**	0.652

BMI = body mass index; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms. Bold type denotes statistical significance.
* Spearman's correlation coefficient.

of IL-17 was decreased in a group of psychotic patients.[31] The authors stated that increased anti-inflammatory/immunosuppressive activity in schizophrenia may reverse or reduce continuing pro-inflammatory processes and chronic inflammation downregulation. Given that gal-3 is expressed mainly in microglia in chronic CNS illnesses and that inflammation might play a part in the pathogenesis of schizophrenia, our findings are consistent with the neuroinflammation hypothesis of schizophrenia.

Another important finding of the present study was the significant positive correlation between SANS scores and serum gal-3 levels. However, the correlation between gal-3 and other clinical parameters was not significant. To the best of our knowledge, only one study has examined the correlation between gal-3 and clinical parameters in schizophrenia patients. Unlike our results, Kajitani et al. found that serum gal-3 levels were positively correlated with positive symptom scores and negatively correlated with negative symptom scores.[19] One possible explanation for this discrepancy is that the relationship between serum gal-3 levels and SANS scores in schizophrenia changes according to cytokine levels. Previous investigations have shown that the serum levels of some cytokines, such as IL-1β and IL-6, are positively correlated with negative symptoms from the Positive and Negative Symptoms Scale in schizophrenia patients.[32-34] Some studies have found that gal-3 regulates the expression levels of cytokines such as IL-1β and IL-6, which are related to the negative symptoms of schizophrenia.[35,36] Thus, increases and decreases in cytokine concentrations associated with schizophrenia symptoms might explain the connection we found between serum gal-3 concentrations and negative symptoms of schizophrenia. The impact of physical activity on gal-3 circulation could be another possible mechanism underlying the correlation of gal-3 and SANS subscales. Issa et al. recently found that physical exercise leads to increased gal-3 levels in rheumatoid arthritis patients and healthy controls, as well as that the cartilage protein oligomeric matrix could induce higher serum gal-3 levels following physical exercise.[37] It is not surprising that we found low levels of gal-3, especially since schizophrenia patients with negative symptoms tend to have inadequate physical exercise levels.

Among the CNS changes in schizophrenia that represent possible neural distortions, the theory of dopaminergic dysregulation is currently the most significant.[38] Tyrosine hydroxylase (TH) is a crucial enzyme in dopamine biosynthesis that acts as a significant signaling molecule in the CNS. Several transcription factors regulate the expression of the TH gene, the most important of which is the cAMP response element-binding protein (CREB).[39] Wu et al. found that the transcription factors CREB1a, 1b and 3 all were significantly upregulated by gal-3 transfection.[18] Gal-3 was shown to promote transactivation of transcription factors, such as CREB, and induce promoter activity by enhancing or stabilizing the transcription factor binding to the cAMP response component sites in the promoter site of target genes.[18] Gal-3 was shown to control CREB and influence TH gene expression at both high and low concentrations.[18] Therefore, via CREB, gal-3 can enhance the expression of the TH gene. Based on this information, the low gal-3 levels in our schizophrenia patients suggest that gal-3 may have an important role in the etiology of schizophrenia. Thus, it is a significant finding that patients with schizophrenia had lower serum gal-3 concentrations than controls.

The present study had several limitations. First, the sample size was relatively small, and our findings may not be generalizable to a broader community. Second, the possible impact of antipsychotics on cytokine profiles cannot be excluded, so the influence of various antipsychotic drugs should be further evaluated for these particular biomarkers. Third, it is worth noting that some confounding factors linked to outpatient habits, i.e. lifestyle, exercise, and nutritional alterations, could influence serum gal-3 concentrations. Finally, another limitation was the absence of anti-inflammatory markers other than gal-3.

Decreased concentrations of serum gal-3 may suggest inflammation, proapoptotic activation, and impaired neurodegeneration in schizophrenic patients. There was also an association between gal-3 serum concentrations and SANS scores. Given its detectable serum concentration, gal-3 could serve as a biomarker for schizophrenia that should be assessed in a cohort study and, possibly, in future clinical trials.

Disclosure

The authors report no conflicts of interest.

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