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Brain-Derived Neurotropic Factor Serum Level and Severity Symptom of Bataknese Male Patients with Schizophrenia in North Sumatera, Indonesia

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Abstract

BACKGROUND: Schizophrenia is a severe mental disorder that is multi-causative and multi-factor, generally affecting about 1% of the population. The elevation level of brain-derived neurotrophic factor (BDNF) offers several protections from other neurodegenerative processes that occur in schizophrenia since this deficit of neurotrophic factors can contribute to changes in brain structure and function that underlie the schizophrenia psychopathology.

AIM: To analyse the correlation between BDNF serum levels and symptom severity by using the Positive and Negative Syndrome Scale (PANSS) instrument in Bataknese male patients with schizophrenia

METHODS: This study was a correlative analytical study with a cross-sectional approach using the Positive and Negative Syndrome Scale (PANSS) instrument to assess symptom severity with 60 subjects of Bataknese male patients with chronic schizophrenia. Moreover, this research was conducted at the Psychiatric Hospital of Prof. Dr M. Ildrem Medan, Indonesia. BDNF serum was analysed with the Quantitative sandwich enzyme immunoassay technique by via Quantikine ELISA Human CXCL8/IL-8 HS. Also, the data analysis was performed through Spearman's correlative bivariate analytics using SPSS software.

RESULTS: A negative correlation between the BDNF serum level and the negative scale PANSS score in men with schizophrenia ($r = -0.820$, $p < 0.001$) was found. Moreover, there is a negative correlation between BDNF serum levels and PANSS total scores in men with schizophrenia ($r = -0.648$, $p < 0.001$)

CONCLUSION: BDNF serum level in Bataknese male patients with schizophrenia has a relationship that affects the severity of symptoms in schizophrenic patients, especially for negative symptoms.

Introduction

Schizophrenia is a common psychotic disorder, with a risk of around 1%. The most frequent initial onset of this disorder is the age of 15-30 years and is a chronic disease that disrupts patients and their families. Moreover, it has a major impact on society and economy [1]. Schizophrenia patients experience complex mental deterioration disorders. The mechanism that causes this disorder is still unclear, but some evidence shows that the cause is multi-causal and multi-factors. These factors include genetic, neuro-developmental, social [2], [3], [4], [5], [6] and immune factors [7]. On the other hand, schizophrenia is not a static mental disorder but a dynamic process that causes dysregulation of various pathways [8]. Other factors that are suspected of having a role in the presence of a degenerative central nervous system (neuro-degeneration) [9].

The aetiology and pathophysiology of schizophrenia have not been explained so far. Various changes in the central nervous system can cause clinical manifestations of the disease. Neurotransmitter deficits are considered as epiphenomena underlying the disorganisation of neurotropins [10]. Brain-Derived Neurotropic Factor (BDNF), a member of the neurotropic derivative, is often found in adult mammalian brains and plays an important role in the development, regeneration, survival, maintenance and function of neurons [11], [12]. During the development, BDNF plays an important role in maintaining proper axonal growth.

BDNF is also essential for the development and survival of dopaminergic, serotonergic, GABAergic, and cholinergic neurons. Also, there are significant roles in the pathophysiology of psychiatric diseases, including schizophrenia [13].

Furthermore, BDNF plays an important role in the mesolimbic dopaminergic system and regulates the expression of D3 dopamine receptors [14]. Finally, BDNF is produced by immune cells in response to neuroimmune and inflammatory response to protect the brain from any damage. Based on this evidence, BDNF turns into a potentially useful biomarker to study the inflammatory features of schizophrenia, which has a role in the persistent negative symptoms and cognitive features in schizophrenia [15]. This suggests that a relationship between BDNF properties with dopamine pathway in schizophrenia [16].

Some studies performed sub-categories of schizophrenia symptoms into 5 parts, positive symptoms, negative symptoms, cognitive symptoms, aggressive symptoms and depression/anxiety symptoms [1]. Negative symptoms of schizophrenia are characterised by the deficits in normal emotions and social functions that can be primary or secondary for the treatment of diseases or other manifestations. These symptoms are strongly associated with long-term paralysis that tends to worsen over time and negatively affect the patient's quality life. Despite this burden, negative symptoms are more resistant to treatment compared to positive symptoms, and existing antipsychotics are not able to reduce the negative symptoms of schizophrenia [17]. In general, Indonesian population is determined to follow the paternalistic line (father/male), for example, the Javanese and Bataknese tribes. In this case, Bataknese male will give offspring who are also Bataknese. The total number of ethnic groups in Indonesia as a whole reaches more than 1,300 ethnic groups. In addition to the various types, the number or size of the population of each type of ethnic group is also very varied [18]. In this study, the subjects chosen were Bataknese. The author was interested in choosing the Bataknese because the majority of schizophrenia patients who were hospitalised in the psychiatric hospital, Prof. Dr M. Ildrem in North Sumatra is Batak tribe.

To sum up, this study is aimed to investigate the relationship between BDNF serum levels and symptom severity measured using the PANSS instrument in Batak male patients with chronic schizophrenia.

Methods

This study performed a cross-sectional study design to evaluate the relationship of BDNF serum level as of symptoms severity as measured by PANSS in Bataknese male patients with schizophrenia. The total sample of this study was 60 people, collected using the consecutive sampling method. Furthermore, this study has followed the Medical Ethics Committee of Universitas Sumatera Utara, Medan, Indonesia.

Participants: A total of 60 subjects with schizophrenia were established by structured interviews using the MINI ICD-10, which was hospitalised at the Psychiatric Hospital of Prof. dr. M. Ildrem, Medan, Indonesia.

Inclusion criteria: Age between 20-60 years, bataknese male, smoking, chronic schizophrenia patients for 2 years with stabilisation phase (PANSS 60-80 score), understanding Indonesian language, willing to be a respondent and able to be interviewed.

Exclusion Criteria: Having other mental disorders, suffered from neurologic diseases, history of alcohol use and other substances except for tobacco.

Data collection was preceded by screening using inclusion and exclusion criteria. Individuals who met the inclusion criteria and exclusion criteria were asked for approval to take part in the study after obtaining informed consent. Then, the demographic data of the subject were filled PANSS score assessment on the research subject was performed. The next stage was as much as 5 ml of the subject's blood samples were taken by laboratory officers who will then be examined in the laboratory to obtain the result of BDNF serum level.

Measurement

The severity was measured through the Positive and Negative Syndrome Scale (PANSS). It was developed in the late 1980s aimed at assessing clinical symptoms of schizophrenia. PANSS contains 30 items in three subscales, seven items include positive symptoms (for example, delusions and hallucinations), seven items include negative symptoms (for example, social withdrawal, flat affect, lack of motivation), and 16 items include general psychopathology (for example, anxiety and depression). Assessment can be completed in 30 to 40 minutes. The reliability is good, and the validity is very good [19]. In previous PANSS examination, the former of the researcher was trained with an interpreter, which then PANSS score will be conducted with a suitability test between the researcher and the interpreter.

BDNF was assessed by taking 5 ml of the subject's blood samples by laboratory personnel in the morning at around 8 am, which will then be examined in the laboratory to obtain the results of BDNF levels. BDNF serum levels were analysed with the Quantitative sandwich enzyme immunoassay

technique by the use of Quantikine ELISA Human CXCL8/IL-8 HS.

The sample used was a human serum. The standard calibration range is 62.5-4000 pg / mL. The limit of detection is 20 pg / mL, and the dilution factor is 20 times. The results have been multiplied by a dilution factor. Measurements using the Microplate Reader Biorad model 680 instruments (Bio-rad Laboratories Inc., CA, USA) with the Microplate Manager version 5.2.1 software (Bio-rad Laboratories Inc., CA, USA).

Data Analysis

The normal distribution test was performed through the Kolgomorov-Smirnov test. Moreover, the analysis between BDNF serum levels and each PANSS score item was conducted using the Spearman's correlative bivariate analytic (N = 60, $Z\alpha$ 5%, Z_β 20%) with SPSS 22 software (SPSS Inc, Chicago, Illinois, USA), and $p < 0.05$ was considered as statistically significant.

Results

A total of 60 research subjects were analysed. In Table 1, the demographic characteristics of the research subjects are described. The average age of the study subjects was 37.65 years with a standard deviation of 6.58 years.

Table 1: The demographic characteristic of the research subject

Variable	Mean/f	SD/%
Age	37.650	6.581
Educational Background		
Junior High school	17	28.3%
Senior High school	41	68.3%
Diploma	2	3.3%
Marital Status		
Not married	19	31.7%
Married	41	68.3%
Smoking Level		
Current smokers	31	51.7%
Former smokers	21	35.0%
Never smokers	8	13.3%
Relapse	3.417	0.497
Body Mass Index	22.232	1.543

Mean/f: Mean/Frequency; SD/%: Standard Deviation/Percentage.

The highest level of education is a senior high school with 41 people (68.3%). Most subjects are married (68.3%) and 51.7% of samples are a current smoker. Furthermore, the mean of relapse was 3.417 (SD = 0.497), and the average Body Mass Index is 22.232 (SD = 1.543).

Table 2: The BDNF serum level and PANSS score

Variable	Mean ± SD
BDNF serum	24.573 ± 4.035
PANSS Positive score	11.050 ± 2.118
PANSS negative score	26.783 ± 3.923
Psychopathology general PANSS score	31.466 ± 3.202
Total PANSS score	69.300 ± 6.181

In Table 3, it can be seen that a negative correlation between BDNF level and PANSS scores is discovered. There was a strong and significant correlation between BDNF serum levels and negative PANSS scores ($r = -0.820$, $p < 0.001$) and between BDNF serum levels and PANSS total scores ($r = -0.664$, $p < 0.001$). Moreover, a very weak correlation between BDNF serum level and positive PANSS score and PANSS score general psychopathology is recorded.

Table 3: The correlation between BDNF and PANSS

	PANSS Score	Coefficient Correlation (r)	*p*
BDNF	PANSS Positive score	-0.155	0.237
	PANSS negative score	-0.820	< 0.001*
	Psychopathology general PANSS score	-0.140	0.287
	Total PANSS score	-0.648	< 0.001*

*Spearman correlation ($p < 0.05$).

Discussion

The main finding in this cross-sectional study was a negative correlation between BDNF serum levels and negative scale PANSS scores in Bataknese male patients with schizophrenia and a negative correlation between BDNF serum levels and PANSS total scores. This study is by Akyo et al., (2015) which concluded that there were negative correlations between BDNF peripheral measured levels and the symptomatology of schizophrenia. BDNF plays an important role in the development of the central nervous system. It has an impact on the serotonergic signalling, glial cells, hippocampus neurons and the brain cortex. Moreover, BDNF, in contrast to other neurotrophins, is secreted in response to neuron excitation and releasing dopamine and glutamate from the hippocampal cells. BDNF expression in the frontal cortex can be regulated via dopaminergic receptors [20,21]. Koeva (2014) discovered that changes in the neurotrophic factor system were one of the factors considered in the pathological cascade of schizophrenic psychosis. The decreased BDNF serum levels show a potential deficit in the release of neurotrophic factors in patients with schizophrenia. The results of this study support the view that BDNF is related to schizophrenia [10].

Furthermore, this study is also by the study of Sasha (2018), found that the levels of BDNF serum were associated with negative symptoms in older adults with schizophrenia. She found that the higher BDNF serum level and greater severity of negative symptom items [13]. Recently, Niitsu et al. (2014) investigated BDNF levels in patients with schizophrenia. They reported that the serum was mature and had a positive correlation between BDNF serum levels and negative symptoms. They concluded that the mature BDNF might not be a good candidate

as a biomarker in schizophrenia [22].

According to Zhang et al., (2010), an increase in BDNF levels protects the neurodegenerative processes that occur in schizophrenia, since this deficit of neurotrophic factors can contribute to changes in brain structure and function underlying the psychopathology of schizophrenia [11]. The nervous development of abnormalities and dopamine dysregulation systems have been implicated in the pathophysiology of schizophrenia. Therefore, BDNF can be a marker of abnormal nerve development and neurotransmission in schizophrenia [23]. The BDNF serum levels are widely measured in numerous psychiatric disorders, and the use of BDNF plays a role in the treatment of many psychiatric disorders [20].

In contrast to Fernandez et al. (2015), peripheral BDNF levels in serum and plasma were slightly reduced in Schizophrenia compared to controls. In particular, this decline is emphasised by the duration of the disease. However, the rate of decrease in peripheral BDNF levels did not correlate with the severity of positive and negative symptoms. In plasma, but not serum, peripheral BDNF levels consistently increase after the antipsychotic treatment regardless of the patient's response to treatment [24].

For BDNF itself, there are many factors that contribute to influence, such as gender, smoking habit, body mass index, etc. In this study, the recruited subjects were male patients, where previous studies have stated that gender affects serum BDNF levels. Estrogens have multiple functions in the brain. Pluchino et al. (2013) showed that estrogen could regulate the expression of BDNF via the estrogen response element on the BDNF gene. Another group also indicated that BDNF mediated the effects of testosterone on neuronal survival [25]. In the baseline data, it is found that the most current smokers are 31 people (51.7%) as in the study of Zhang and colleagues found a significant association between BDNF levels and negative symptoms of schizophrenia with a further link to nicotine. Because the negative symptoms of schizophrenia are associated with hypoactivity of the dopaminergic system, smoking can reduce negative symptoms by increasing dopamine in the nucleus accumbency. Also, BDNF increases the release of dopamine in the mesolimbic dopamine system and induces dopamine-related behaviours [11].

For Body Mass Index, the subjects selected were in normal-weight categorisation, considering previous studies by Lommatzsch et al., (2005) shown that plasma BDNF levels in people health decrease significantly with weight gain [26]. Araya et al., (2008) also emphasized the relationship between weight and plasma BDNF levels in overweight and obese people who had gone on a diet, where BDNF levels increased after 3 months on a diet [27].

This study has decided that Batak tribes were chosen. Whether there is a connection between the Bataknese male patients and BDNF serum levels, it still needs further and deeper research. Previous research stated that there were 2 types of sequences of Batak ethnics especially in BP 113-116 were observed. Also, it was expected that Batak ethnicity had a tradition to keep their purity by marrying their relative would show a similar sequence. However, no similarity was found. The reason of these phenomena could be resulted by some Bataknese man married with other race, but they adopted their wife or husband into ethnic Batak by adding a Batak's surname. Interestingly, batak ethnic with ATCG sequences were categorized to have higher risk for having schizophrenia [28].

In this study, a strong and significant correlation has been discovered. There is a negative correlation between BDNF serum level and negative PANSS score in Batak male schizophrenia patients ($r = -0.820$, $p < 0.001$) in the sense that the higher the severity of negative symptoms in Schizophrenic patients, the lower serum BDNF levels. In this study there was also a negative correlation between BDNF serum levels and PANSS total score in Bataknese male patients with schizophrenia ($r = -0,648$, $p < 0.001$).

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Ethical Aspects

Authors state that there is no conflict of interest to this research and the procedure conducted has followed the ethics regulated by Universitas Sumatera Utara.

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