BDNF (brain-derived neurotrophic factor) serum levels in schizophrenic patients with cognitive deficits

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Abstract. Schizophrenia is a complex neurodevelopmental disorder with cognitive impairment as the main part. BDNF regulates aspects of developmental plasticity in the brain and is involved in cognitive function. Cognitive functions include capabilities such as attention, executive functioning, assessing, monitoring and evaluating. The aim of the study was to know the BDNF levels in schizophrenic patients with cognitive deficits. The study was held in October 2016 - March 2017, and was the first in Indonesia, especially in North Sumatra. The study was approved by the medical ethics committee of the University of North Sumatera. The study is descriptive based on a retrospective method with cross-sectional approach. The subject is 40 male schizophrenia. Cognitive deficits were assessed by MoCA-Ina. BDNF serum levels were analyzed using the quantitative sandwich enzyme immunoassay. The average MoCA-Ina score is 21.03±5.21. This suggests that there is a cognitive function deficit in schizophrenic patients. The mean serum BDNF level was 26629±6762. MoCA-Ina scores in schizophrenic patients <26 who experienced a deficit of 77.5% and serum BDNF levels with normal values ranging from 6.186 to 42.580 pg/ml.

1. Introduction
Schizophrenia is a complex neurodevelopmental disorder with cognitive dysfunction as a major part, based on a number of studies conducted on patients suffering from schizophrenia with clinical symptoms and the patient's social function is a consequence of cognitive neurodeficits. Cognitive deficits are a core aspect of schizophrenia.[1] Schizophrenia is characterized by positive and negative symptoms that can affect the patient's mind, perception, speech, and behavioral influences. Positive symptoms include hallucinations, voices that speak to or around the patient, and delusions that are often paranoid. Negative symptoms include flattening effect, loss of pleasure, loss of will, and social withdrawal.[2] The prevalence of schizophrenics is generally estimated to be around 1% worldwide. Based on a Saha et al. study showing from 188 studies drawn from 46 countries found a lifetime risk of 4.0 per 1000 inhabitants; the estimated prevalence of the least developed countries is significantly lower than that of countries classified as developing or developing countries. Immigrants to developed countries show increased rates of schizophrenia, with the risk of expanding on the next generation.[3]

Research over the last two decades has shown a cognitive performance relationship with the neurotrophin system. Neurotrophin is a family of polypeptide growth factors with similar structures, involved in the process of brain development, differentiation and survival of neurons, synaptic plasticity, and connectivity. The neurotrophin group consists of Nerve growth factor (NGF), derived
from Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3), Neurotrophin 4/5 (NT-4/5).[4]

Laing et al. in 2012 assess the relationship of cognitive function: psychomotor speed, attention, and memory with BDNF polymorphism (rs6265, rs7103411 and rs7124442). The results showed there was a relationship between BDNF polymorphism (rs7103411) and memory. In addition, gender-specific analyzes reveal a relationship of BDNF polymorphism (rs7103411 and rs6265) with psychomotor speed and memory in women.[5]

Zhang et al. in 2012 examined a group of recurrent schizophrenic inpatients for assessment of neuropsychological status (RBANS) and assessed BDNF Val66Met polymorphism and serum levels of BDNF. This study discovered the association between variant BDNF Met and poor visuospatial performance / construction and attention reduction in schizophrenic patients. They also found that there was a relationship between decreased serum levels of BDNF and cognitive impairment in schizophrenia depending on Val66Met BDNF polymorphism.[6]

So through this study wanted to know BDNF levels in patients with schizophrenia cognitive deficit in Indonesia.

2. Material and Method
The type of research used is a descriptive study based on a retrospective method with cross-sectional study approach, which assessed the level of BDNF serum in schizophrenic patients with cognitive deficits.

This research was conducted at the inpatient installation of Mental Hospital Prof. Dr. M. Ildrem Medan the period October 2016 - March 2017. The population was schizophrenic patients, while the affordable population was schizophrenic patients at the Inpatient Installation of Mental Hospital Prof. Dr. M. Ildrem Medan. Sampling method by Non-probability sampling type consecutive sampling that is all subjects that come and meet the selection criteria as much as 40 people.

Researcher Conduct a PANSS assessment of the subject. all the subjects of the study (schizophrenic patients were collected for 5 ml of blood sampling before taking ± 12 hours of medication by private laboratory personnel until the desired number of subjects was met, which would then be examined in a private laboratory to obtain serum BDNF levels. BDNF serum levels were analyzed using the quantitative sandwich enzyme immunoassay. After performing blood sampling, assessment and calculation of the Montreal Cognitive Assessment Scale of Indonesia (MoCA-Ina) were performed on the patient.

Data analysis analyzed statistically descriptive. The data will then be presented in the form of tables and narrations according to the variables studied.

3. Result
The demographic features of schizophrenic patients are presented in Table 1. Variables with categorical scales are presented in frequency and proportion.

| Variable         | N  | %  |
|------------------|----|----|
| Age, years       |    |    |
| 20 - 30          | 1  | 2.5|
| 31 - 40          | 25 | 62.5|
| 41-50            | 10 | 25.0|
| 51-60            | 4  | 10.0|
| Education        |    |    |
| Junior high school | 10 | 25.0|
| Senior High School | 27 | 67.5|
| Diploma          | 3  | 7.5|
| Marital status   |    |    |
Table 1 shows that the proportion of patients with schizophrenia is 20-30 years (2.5%), 31-40 years (62.5%), 41-50 years (25%), and 51-60 years (10%). In the study of Ayano in 2016 states that the onset of schizophrenia usually occurs between late adolescents and mid 30 years. For males, the peak age of onset for the first psychotic episode is in early to mid 20 years.[3]

The proportion of schizophrenic patient education is SMP (25%), SMA (67.5%), D3 (7.5%). In Zhang's study in 2012, it found that the demographics of schizophrenic patients were based on education with a mean of 9.9 and standard deviation of 6.2. The marital status is unmarried (51%), marriage (27.9%) and divorce (21.1%).[7] The proportion of marital status of schizophrenic patients is unmarried (40%) and mating (60%). Based on the length of illness schizophrenia patients are 2-5 years (50%) and >5 years (50%).

Table 2. MoCA-Ina score in schizophrenic patients.

| Variable | Mean | SD  | P    |
|----------|------|-----|------|
| MoCA-Ina | 21.03| 5.21| 0.078|

*Shapiro-Wilk test*

Table 2 shows that the Moca-Ina score with the mean of 21.03 and the standard deviation of 5.21. This suggests that cognitive function in schizophrenic patients is impaired, shown by MoCA-Ina's normal score is 26. In the 2012 Fisekovic study found the average MoCA score of 19.9 with standard deviation 5.1 in 30 schizophrenic patients with 50% of male schizophrenic patients and 50% of whom are female schizophrenics.[1] Research by Ramirez et al. in 2014 found MoCA scores in 100 schizophrenic patients was 23.0 with standard deviation 3.9 in which the subjects in the study were 65% were male and 35% female.[8]

Table 3. Distribution of cognitive function in schizophrenic patients.

| Cognitive function | n  | %   |
|--------------------|----|-----|
| Normal (≥ 26)      | 9  | 22.5|
| Abnormal           | 31 | 77.5|
| Score              | 40 | 100 |

Table 3 shows that the proportion of cognitive schizophrenic patients is normal (≥26) (22.5%) and abnormal (77.5%). Studies conducted by Lezak et al. in 2012 indicate that psychomotor speed has been associated with the speed of nerve conduction, the speed of information processing and data retrieval from Jensen's memory in 1993. This is an influence on the cognitive domain.[9]

Cognitive impairment often occurs in schizophrenia, which affects up to 75% of patients and only 27% is classified as "normal" neuropsychopathological. This suggests that cognitive impairment in schizophrenic patients is significantly normal.[10]

Table 4. Serum BDNF (brain-derived neurotrophic factor) in schizophrenic patients.

| Variable | Mean | SD  |
|----------|------|-----|
| BDNF     | 26629| 6762|

Based on table 4 serum levels of BDNF (Brain-derived Neurotrophic Factor) with a mean of 26629, standard deviation 6762. From the research results obtained that the level of BDNF value is still
normal that is between 6,186 - 42,580 pg / ml. In the Rowbotham et al study of 2015 found that of 14 studies (910 patients, 717 controls) 8 studies reported a decrease in BDNF levels in schizophrenic patients compared with controls; 3 studies with a total of 274 subjects found 128 subjects with elevated levels of BDNF; while 3 studies with 62 reported no group differences. Meta-analysis of all collected studies confirmed decreased BDNF levels in schizophrenia versus control (medium size effect); however, the group differences were not significant, the study used cases without treatment.[11]

Research conducted by Laing et al. in 2012 assessed the association of cognitive function: psychomotor speed, attention, and memory with BDNF polymorphism had a significant relationship p (0.007) <0.05.[5] Results of the study ever conducted by Miyajima et al. in the year 2008 states that BDNF polymorphisms found to be associated with general intelligence have a significant relationship p (0.008) <0.05.[12]

4. Discussion

In Ben Gal's 2016 study in 38 patients (35 men and 3 women) linked that schizophrenia was associated with neuropsychological deficiency. The typical neuropsychological profile of schizophrenia is characterized by deficits in memory and learning, abstraction, executive function, information processing speed, and attention. The researchers examined the neuropsychological function of people suffering from schizophrenia as well as other mental disorders. All the groups showed low scores in memory, executive function, attention, and information processing speed, as well as with schizophrenia showing a much greater decrease in all cognitive areas. Ben Gal's study found variables that may affect cognitive functioning that reveals significant age associations, first episodes of illness and hospitalized time with correlations between these variables and the rate of capture score.[13]

The decreased cognitive function is a major manifestation of schizophrenia, and cognitive dysfunction has been identified as a key determinant of long-term quality of life. The difficulties experienced by schizophrenic patients to live independently and to gain job competitiveness are largely due to cognitive dysfunction. Cognitive impairment has emerged as an important new target in schizophrenia.[14]

In the 2013 Nieto study proves that the brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the brain, and has been associated with several psychiatric disorders that show that schizophrenia is a brain development disorder and plasticity. The role of BDNF in neural development, synaptic regulation, and synaptic plasticity has been linked as a candidate to explain part of the pathogenesis of this disease. Changes in neurotrophic factors such as BDNF and gene levels may contribute to the development of brain changes, synaptic disconnectivity, and failure in neuroplasticity, and explain at least some of the morphology and neurochemistry and abnormalities found in the brains of patients with schizophrenia. BDNF may play a role in the pathogenesis of schizophrenia, but it also examines evidence demonstrating that it plays a role in the pathophysiology of cognitive deficits.[14]

In the 2012 Zhang study, BDNF was associated with cognition in schizophrenics but not in healthy control, suggesting that the effects of BDNF serum on cognitive function differed between patients with schizophrenia and healthy control. Zhang's study found higher levels of BDNF associated with a better cognitive function in schizophrenia, which is consistent with two recent studies in healthy adults who showed higher levels of serum BDNF associated with the better neuropsychological function.[6]

5. Conclusion

A total of 40 subjects of schizophrenic patients who participated in the study were in the inpatient installation of in Mental Hospital Prof. Dr. M. Ildrem Medan October 2016-March 2017.

Based on demographic characteristic, it was found that the subjects of the study were age group 31-40 years old for 25 subjects (62.5%), based on the highest level of education were 27 subjects (67.5%), based on the highest marital status with marital status of 24 subjects (60%) and based on 2-5 years old sickness of 20 subjects (50%) and> 5 years by 20 subjects (50%).The average score of MoCA-Ina
score in schizophrenic patients was 21.03±5.21. The average serum BDNF level in schizophrenic patients was 26629±6762.

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