ID Design
P r e s s

The Relation of Brain-Derived Neurotropic Factor (BDNF) Serum Level to Sub-Domain Cognitive Functions of Indonesian Schizophrenia Patients Measured by MoCA-Ina

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Abstract

BACKGROUND: BDNF implies to the development of abnormal nerves and neurotransmission that occurred during the changes of cognitive functions. However, in determining initial diagnosis of schizophrenia, measurements focus on the presences of positive and negative symptoms, and general psychopathological features without concerning the BDNF serum, which involves in central nervous system as the main symptom of schizophrenia.

AIM: To determine the relation of BDNF serum level to cognitive functions of schizophrenia patients based on sub-domain of Montreal Cognitive Assessment Indonesia Version (MoCA-Ina)

METHODS: This study was carried out based on observational analysis with cross-sectional design study. The samples were collected by non-probability sampling and consecutive sampling by recruiting 65 of male schizophrenia patients at Prof. Dr. M. Ildrem Mental Hospital, Medan, North Sumatera, Indonesia. BDNF serum levels were analysed throughout quantitative sandwich enzyme immunoassay method, while the cognitive functions were conducted by performing the MoCA-Ina, which concern to attentions and concentrations, executive function, memory, languages, visuoconstructional abilities, numerical calculation, and orientation.

RESULTS: The serum level of BDNF was accounted averagely for 27161.26, with 5350.37 of standard deviation. There was positive correlation with medium strength (r = 0.4 - < 0.6) in visuospatial function, attention (r = 0.437), and memory (r = 0.413).

CONCLUSION: Relation between BDNF serum level and cognitive function occurred in visuospatial, attention and memory domains based on MoCA-Ina assessment.

Introduction

Cognitive impairment is experienced by almost 70% of schizophrenia patients, while the rest of that number is classified as schizophrenia patients with neuropsychopathologically normal. This event shows significantly that cognitive dysfunction in schizophrenia patients is a normal condition. The dysfunctional of cognition is detected before the diagnosis of schizophrenia in which every cognitive domain is influenced particularly in memory, attention, motoric abilities, executive function, and intelligence. This dysfunction is also affected the social function and functional results [1] of the individuals which cognitive disabilities and functional disturbance are commonly found in schizophrenia individuals. It has been reported that the treatment of cognitive abilities had the potential in altering, and positive correlation of BDNF serum level to the functional abilities of schizophrenia patients, particularly in their memory [4], [5]. However, a few studies have been carried out merely in investigating the relation of BDNF to cognitive function, specifically to basic learning abilities including image projections, reading, writing, calculating, verbal memory, and visual perception. The knowledge about learning function of schizophrenia patients as well as its relation to cognitive functions and impairments is important to be understood due to the possibilities in mapping the academic competence of patients and effective intervention plan.

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Studies that have been carried out in the recent two decades provide the relation of cognitive performance and neurotrophin system. This system is one part of systems that play important role in the growth factor of polypeptide, which involves to the brain development, differentiation and life expectancy of neurons, synaptic plasticity and connectivity. The neurotropic group consists of nerve growth factor (NGF), which is originated from the derivation of brain neutrophil factor or brain-derived neutrophil factor (BDNF), neurotrophin-3 (NT-3), neurotropic 4/5 (NT4/5) [3]. Many studies have reported that relationship between BDNF variants and cognitive functions such as psychomotor speed, attention and memory [7], poor visuospatial performance, decreased attention [20] occurred among schizophrenia patients. Other studies have also found that the decrease in BDNF serum levels and cognitive impairment in schizophrenia patients have been reported to be depending on the polymorphisms of BDNF Val66Met4, rs6265, rs73103411 associated with memory [7], and rs7124442 [7]. On the other hand, in a study conducted in 2013, psychosis patients were reported to have a positive relationship between BDNF plasma and five cognitive domains which were learning ability, immediate and delayed memory, abstract thinking and processing speed, in which occurred during 6 months of monitoring. This relation persisted after the controlling of prescribed medication, drug consumption, intelligence quotient (IQ), and negative symptoms that were appeared. However, in a healthy control group, the BDNF levels were not associated with cognitive test results [8]. Post-mortem studies to the tissue brain of schizophrenic patients have reported that the BDNF mRNA and protein levels showed significant changes within the cerebral cortex, anterior cingulated cortex, and hippocampus parts of the patients compared to those who were healthy. The same study also reported that the BDNF levels reduced significantly in schizophrenic patients although those were not in blood composition, and the correlation of the level dosages of antipsychotic clozapine occurred [9].

BDNF performs importantly in cognitive functions, which was investigated firstly in cellular and molecular study. It has been reported that the BDNF secretion is a necessity for long-term potentiation (LTP) and long-term depression (LTD), which occurred as cellular mechanisms for learning and memorizing. The changes of neurotropic factor such as BDNF and gene levels can contribute to the development of brain, synaptic disconnection and failure in neuroplasticity, and at the very least it can explain the half morphological and neurochemical of brain failures found in schizophrenic patients. For instance, a study conducted in 2013 has reported that BDNF was distributed mostly in the brain, and it was related to several mental disorders which implied to the impairment of brain and plasticity developments of schizophrenic patients [6]. This factor also involves in schizophrenic pathogenesis, and it also shows the

deficit of pathophysiological cognitive which can be considered as the main symptom of schizophrenia. Based on the previous explanations, literature review has shown no studies that have been carried out in Indonesia, particularly for schizophrenic patients from Medan to provide clinical information to both practitioners and psychiatrists about the relation of cognitive domains to the BDNF serums level of schizophrenia patients assessed from MoCA-Ina.

Research Methodologies

Participants

Research samples in this study included 65 people with schizophrenic disorder. All subjects based on inclusion and exclusion criteria were inquired for the permission throughout informed consent in following this study. After receiving the permission, the recruited inclusion samples were male schizophrenic patients which were diagnosed based on Indonesian Guidelines of Classification and Diagnosis and Mental Health Disorders III (PPDGJ III) within ages in between 20 to 60 years old. According to the first step in determining the diagnosis, structured interviewed based on Mini International Statistical Classification of Diseases-10 (Mini ICD-10). To determine the cognitive functions of the participants, Indonesian version of MoCA measurements which have been validated based on transcultural characteristics were performed [12].

Whilst, the inclusion participants were schizophrenic patients who have been experiencing this disorder for over two years of stable phase of medication. This phase is in remission stages which aim to prevent relapse and to support the increase of cognitive functions. The measurements of PANSS to the research subjects aim to assess the clinical symptoms of schizophrenia, therefore, samples were those who had PANSS score ≤ 60, have the ability in understanding Bahasa Indonesia (Indonesia language), willing to be interviewed and respondents, the lasted educations were junior high or equivalent to senior high, and tertiary educations. Meanwhile, the exclusion criteria in this study were patients who have been suffering from other health disorders with a history of alcohol use.

The Measurements of BDNF Serum

Subjects were gathered for the blood samples collection. As many as 5 ml of blood samples were carried out 12 hours before taking medications by laboratory medical officers until the required samples. The samples were tested and measured in order to obtain the results of BDNF serum level [10]. The serum levels of BDNF were analysed by performing

the quantitative sandwich enzyme immunoassay. The BDNF levels collected in this analysis were plasma and normal blood clots ranged between 6.186 – 42.580 pg/ ml [11]. Then, 5 cc of bloods were placed into the STT tube to be shaken for obtaining the homogenous features. Afterward, the blood samples were allowed to stand for 30-40 minute, and they were immediately placed into centrifuge with a speed of 3000 rpm for 15 minutes. As a result, the separated samples were obtained, for the serum itself was placed into three sample cups with 0.5 cc. These each three samples based on the participants were stored at $20^{o}C$ to be measured for the value of BDNF serum levels in the blood.

MoCA-Ina Assessment

The Montreal Cognitive Assessment of Indonesian Version (MoCA-Ina) measurements were performed to determine the cognitive functions of subjects. Sub-domains of MoCA-Ina tests were designed as a quick-screening instrument to evaluate light cognitive dysfunctions. Total score of this assessment is 30 points, while ≥ 26 is classified normal [13]. MoCA-Ina assessments are consisted by: 1. Visuospatial, it was assessed by a clock drawing task and three-dimensional of boxes; 2. Executive function, it was assessed by trial making B task, phonemic ability task, and abstract words; 3. Language, it was measured by asking the participant to mentioned three unfamiliar animal pictures which were elephant-rhinoceroses and camels, repeating two difficult sentences, and fluently pronounced two sentences; 4. Attention/awareness, it was measured by giving the continuously attentions based on the knocking detection; 5. Concentration, it was assessed by performing the serial reduction task; 6. Working memory, it was performed by asking the subjects to mention digit numbers forwardly and backwardly; 7. Memory, it was performed by giving short-term memory recall task and delayed recall task; and 8. Orientation, it was measured throughout place and time.

Statistical Analysis

This study is observational analytical study with cross-sectional approach. The normality validation was performed by using Kolmogorov-Smirnov test due to the sample numbers which were more than 50. Then, the data was analysed to obtain the correlation value by performing the SPSS analysis.

Results

Demographic data of Subjects

The demographical description of schizophrenic patients is displayed in Table 1. The variables with categorical scales are shown in frequency and proportion including the average and standard of deviation. According to the Table 1, the proportions of the ages were 13.8% for 20-30 years of age, 53.8% for 31-40 years of age, 26.2% for 41-50 years of age, and 6.2% for 51-60 years of age. The highest population is those who were 31-40 years of age. Meanwhile, the highest percentage for the last educational background was the senior high school which accounted for 72.3%. More than a half of the schizophrenic patients that were recruited within the inclusion criteria were married, and based on the duration of experiencing the schizophrenic disorders were 2-5 years for 52.3%, and 47.7% for over 5 years. The smoking characteristics of the schizophrenic patients were found to be smoking for 41.5% and non-smoking individuals for 58.8%.

Table 1: The Distribution of Participants Based on Demographical Characteristics

Variables	n (individuals)	Percentage (%)
Age		
20-30 YoA*	9	13.8
31-40 YoA*	35	53.8
41-50 YoA*	17	26.2
51-60 YoA*	4	6.2
Education		
Junior High	15	4.6
Senior High	47	72.3
Tertiary Education	3	4.6
Marital Status		
Not-Married	28	43.1
Married	37	56.9
Duration of Illness		
2-5 Years	34	52.3
> 5 Years	31	47.7
Smoking Characteristics		
Smoker	27	41.5
Non-Smoker	38	58.8

Serum Levels of BDNF of the Schizophrenic Participants

The following Table 2 shows the serum level of BDNF with average level of 27161.26 ± 5350.37. Based on the normality validation of the data by using the Kolmogorov-Smirnov test, it was obtained that the p is 0.20 (p > 0.05). Therefore, it can be stated that the data was in normal distribution.

Table 2: The Average Serum Levels of BDNF of Schizophrenia Participants

Variabel	Rerata	SD	p
BDNF	27161.26	5350.37	0.20

The Correlation of BDNF Serum Levels to Six Domains Function

The following Table 3 below highlights the correlation results between BDNF serum levels to cognitive domains of schizophrenic subjects. According to the table, it can be seen that the Spearman's correlation of the BDNF serum levels had the p value in between 0.3-0.35 in executive functions, language and working memory, while on the concentration and orientation domains, both of them had the correlation value over 0.5. In the meantime, the visuospatial, attention and memory domains accounted for 0.001 of p value.

Table 3: Spearman's Correlation Values of Domain Functions

Domain	x̄	BDNF Score	r	p
Visuospatial	2.85 ± 0.83	27161.26 ± 5350.37	0.402	0.001
Executive Functions	2.11 ± 0.75	27161.26 ± 5350.37	-0.132	0.296
Language	4.54 ± 0.83	27161.26 ± 5350.37	-0.120	0.342
Attention	0.62 ± 0.49	27161.26 ± 5350.37	0.437	0.00
Concentration	1.94 ± 0.91	27161.26 ± 5350.37	0.081	0.522
Domain Memori Kerja	1.88 ± 0.33	27161.26 ± 5350.37	-0.124	0.327
Memory	2.32 ± 0.92	27161.26 ± 5350.37	0.413	0.001
Orientation	5.28 ± 0.65	27161.26 ± 5350.37	0.075	0.550

The correlation among domain samples can be determined based on Table 3. On the visuospatial domain, there was positive correlation to the serum level with medium power ($r = 0.4 - < 0.6$) [14], and the same feature occurred to the attention and memory domains. For the orientation, working memory, concentration, language and executive functions, no correlations occurred due to the p value over 0.05.

Discussion

This study is the first study carried out in Indonesia, particularly in Medan, North Sumatera. The aims were to investigate the correlation between the BDNF serum levels to the cognitive functions of schizophrenic patients assessed by the MoCA-Ina.

The Correlation of Demographical Studies and BDNF Serum

The demographical characteristics have reported that the ages were classified into 20-30, 31-40, 41-50, and 51-60 years of old. Based on the results, the highest percentage of schizophrenic patients was found in 31-40 years of old, accounted for over a half, and it was followed by 41-50 years of old for just above a quarter. This implies to the initial schizophrenic disorder occurred in the middle of age of 30s. For the male patients, the highest onset ages for the first episode of psychotic is started in the middle ages of 20 years old [15]. It has been reported that cohort studies of unhealthy teenagers were found no correlation between Va166Met polymorphism to the memory [16], while the other study has reported that the a late adults ages group was observed to have no correlation between polymorphism in the normal aging period of time and the decrease of cognitive functions [17]. The educational characteristics had the highest percentage in secondary schools which accounted over 75%. According to the marital status of the subjects, it was found that schizophrenic disorders were found from those who had married contributed for 56.9%, but this study showed differently to a study that reported schizophrenic patients occurred for non-married status for 51%, married for 27.9%, and divorced for 21.1% [5].

Based on the duration of illness in experiencing the schizophrenic disorders, the durations were 52.3 per cent for 2-5 years, and over five years (47.7%). The longer duration affected the visuo-motoric functions, and delayed visual memory, as it has been reported by a study which aimed to verify whether the duration of illness had the effect for cognitive impairments or another covariates disturbance to the neuropsychological disorders. On the other hand, neuropsychological disorders have been reported to be related to the aging, educational backgrounds, sexes, as well as the treatment status [18]. For the smoking experiences, it was found that 41% of schizophrenic patients recruited for this study were smokers and the others were not smokers. Studies conducted in 2013 and 2012 found that smoking were resulted in influencing the cognitive functions. The act of smoking or nicotine consumption could have repaired several cognitive deficits for the schizophrenic patients as the self-medication. This observation showed that the dysfunction of nicotine acetylcholine receptor signaling might have involved to the etiological cognitive dysfunction to schizophrenia [19], [20]. Zhang et al., 2010 [21], has reported that there was an increase of BDNF serum levels to the smoking schizophrenic patients [21].

The Correlation of BDNF to the Cognitive Functions

According to the Table 2, it was found that the BDNF serum levels with average number of 27161.26 ± 5350.37. Zhang et al., has reported in 2016 which involved 657 of hospitalized schizophrenic patients and 445 of normal patients to determine several factors that might have contributed to the decrease of BDNF of the patients, and those included the clinical status of the patients, the sub-types of recruited schizophrenic patients, and the types, dosages as well as the duration of antipsychotic prescription [4]. On the other hand, Rowbotham et al., [22] 2015 found from 14 studies (910 patients and 717 of patients as a control group) that 8 studies have reported to have decreases of BDNF serum levels to the schizophrenic patients compared to the control; 3 studies with 274 subjects found 128 subjects to have increased BDNF serum levels; the other 3 studies reported no differences of BDNF serum levels among the groups. The meta-analysis of all studies was collected to confirm the decreasing of BDNF levels of schizophrenic patients to be compared to the control group, however, no significant results were found in no medication cases. A study conducted by Djordjevi et al., [23] in 2016 found that the BDNF serum levels were significantly lower (20.38 ± 3.73 ng/mL, P = 1.339 E-05), whereas the NO2 concentration of plasma was significantly higher (84.3 (72-121) mmol/L, P = 4.357E-08) than those who were classified as control healthy (25.65 ± 4.32 ng/mL; 60.9 (50-76) mmol/ L respectively) [23]. Based on the assessment of cognitive function for the eight domains to the schizophrenic patients, it was found positive

correlation with medium power (r = 0.4 - < 0.6) to the visuospatial (r = 0.402), attention (r = 0.437), and memory (r = 0.413). This study implies that there was relation between the BDNF serum levels to the decrease of cognitive functions of schizophrenia patients.

The lower BDNF serum levels are related to the smaller hippocampi and deficient recall functions. The BDNF serum levels as a significant factor are related to the hippocampi and the decreasing of memory recall [24]. A study carried out by Aaron has depicted the importance of BDNF involvement in cognitive process in spatial learning and memory, which showed the significant relations between lower level of pBDNF to smaller hippocampal and deficit recall. The BDNF acts as the acsonal authentic growth, and the intensification of synaptic seems to be mediated by the receptor which is related to BDNF, such as tyrosine-receptor kinase B (TrkB). The role of BDNF as biomarker is not completely determined by the current obtained data and results. For instance, specific toschizophrenic has not been proven yet, but the decreasing of BDNF level serum has also been reported in patients who have been experiencing neuro-degenerative and another neuropsychiatric illness. The findings related to the preservation of pBDNF concentration after training and learning have shown the roles of BDNF as the mechanism which may be relating to the performance during cognitive training [25]. A study conducted by Choon in 2011 [26], a significant genotype effects have been found in verbal memory performance and BDNF (F1.436 = 4.51, p =0.03) and the visuospatial abilities (F1.436 = 4.12, p = 0.04).

BDNF Met variant is related to verbal memory and visuospatial disturbance may have potential implication of medication to schizophrenic patients due to the main and persistent psychosocial disorders such as the cognitive functions of schizophrenic patients [26]. In a study carried out by de Azua et al., [8] in 2013 which involved pyschosis, has reported that a positive correlation between BDNF plasmas and five cognitive domains (including learning abilities, instant and delayed memory, abstract thinking and processing speed) after six months of observation. It is found that strong relation after the consumption of prescribed medication, drugs abuse, intelligence quotient (IQ), and negative symptoms, and the healthy control group, the BDNF level is not related to the cognitive function tests results.

In conclusion, this study involved 65 of schizophrenic patients which were recruited from the Mental Hospital of Prof. dr. M. Ildrem Medan from March 2017 to August 2017. According the findings, there was medium correlation (r = 0.4 - < 0.6) between BDNF serum levels and cognitive functions which were assessed by MoCA-Ina in visuospatial domain, attention, and memory. This study focused on demographical characteristics of the participants without concerning the smoking lifestyles to the

patient which have been reported by previous studies in 2013 and 2012 due to the influence of smoking in affecting the cognitive functions. Smoking or nicotine consumption have been reported to repair several cognitive deficits or it acts as self-medication. This observation shows that the dysfunction within the nicotine acetylcholine receptor signaling may have involved in etiological cognitive deficits in schizophrenia. It is expected that further clinical observation related to drugs and medication could have been designed to investigate their relationship in improving BDNF serum levels whether those are related to cognitive functions or cognitive stimulations of schizophrenic patients.

Acknowledgement

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