

ORIGINAL ARTICLE

Correlation of BDNF, VEGF, TNF- α , and S100B with cognitive impairments in chronic, medicated schizophrenia patients

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Abstract

Cognitive impairment is a prominent cause of disability in schizophrenia. Although antipsychotic drugs can rescue the psychotic symptoms, the cognitive impairments persist, with no treatment available. Alterations of BDNF, VEGF, TNF- α , and S100B have been linked to cognitive impairment in several neurological disorders. However, it remains unclear whether their levels are correlated with the cognitive functions of schizophrenia patients. Forty-one chronic, medicated schizophrenia patients were included in this study. Enzyme-linked, immunosorbent assays were used to measure the serum concentrations of BDNF, VEGF, TNF- α , and S100B. Associations between serum protein levels and various domains of the cognitive functions of the schizophrenia patients were observed. We found significant, positive correlations between serum BDNF and the processing speed and attention levels of the patients. Serum VEGF was also positively correlated with their memory and learning functions. In contrast, serum S100B and TNF- α were negatively correlated with the processing speed and attention of the schizophrenia patients. The findings warrant further investigation of these molecules as potential prognostic markers or treatment targets for cognitive impairment in schizophrenia patients.

KEYWORDS

BDNF, cognitive impairment, S100B, schizophrenia, TNF- α , VEGF

1 | INTRODUCTION

Schizophrenia is a chronic, severe, mental disorder which affects 1% of the worldwide population and requires the highest level of financial support of all mental disorders.^{1,2} Cognitive impairments are symptoms that emerge at an early stage of schizophrenia and persist throughout the course of the illness.^{3,4} Although medications such as

antipsychotics, antidepressants, and mood stabilizers can alleviate the psychotic symptoms, cognitive deficits remain a major cause of disability in schizophrenia patients, with no effective treatment currently available.⁴ Thus, biological indicators that can be used as prognostic biomarkers to predict such impairments would benefit patients.

Several molecules have been proposed for potential use as prognostic biomarkers for schizophrenia.⁵ Among those, brain-derived

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neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) have been widely studied. BDNF is a major regulator of several key processes in the brain, including neuronal differentiation, neurite outgrowth, neurotransmission, synaptic plasticity, and cell survival.^{6,7} Genetic polymorphisms of the BDNF gene result in an imbalance of BDNF levels. This has been shown to cause alterations to receptor responses, abnormal neuronal developments, disruptions of neurotransmission, and eventually, cognitive impairment.⁶ Although BDNF is known to be involved in cognitive performance, its levels, polymorphism, and cognitive correlations with schizophrenia remain inconclusive.⁸⁻¹²

VEGF is known to play important roles in regulating cerebral blood flow, neurogenesis, and neuronal plasticity.^{13,14} In humans, low-serum VEGF was found in both drug-naïve and medicated, first-episode, schizophrenia patients. This also correlated with declines in neurocognition and social cognition, compared with healthy controls.^{15,16} In contrast, some studies reported that the serum VEGF levels of chronic, medicated schizophrenia patients were unchanged¹⁷ or increased.¹⁵ In addition, the elevated serum VEGF levels found in chronic schizophrenia have been shown to be related to prefrontal cortex volume reductions measured by magnetic resonance imaging.¹⁸ Thus, the level of VEGF and its correlation with cognitive functions in schizophrenia remain controversial.

Besides a neurotrophic imbalance, an inflammation hypothesis has been strongly proposed as a pathogenesis of schizophrenia. Several studies suggested that alterations of inflammatory cytokines cause brain volume reduction, neuronal toxicity, neurotransmission disruption, psychotic behaviors, and cognitive deficits^{5,19,20} (Thomas A.^{21,22}). Among those cytokines, tumor necrosis factor alpha (TNF- α) and S100 Ca²⁺-binding protein B (S100B) were widely mentioned as major contributors to neuroinflammation in schizophrenia.^{23,24} TNF- α is a well-known, pro-inflammatory cytokine. An appropriate level is required to maintain its critical roles in cognitive abilities.²⁵ Previous studies have revealed an elevation of peripheral TNF- α levels in both first-episode and medicated schizophrenia patients.²⁶⁻²⁸ These rises were related to symptom severities and declines in working memory.²⁹ In addition, antipsychotic treatment has been shown to reduce TNF- α levels in schizophrenia.^{26,30} Conversely, some studies found a decrease in serum TNF- α in chronic schizophrenia patients. The decrease correlated with executive function deficits and Positive and Negative Syndrome Scale cognitive scores of patients,^{31,32} suggesting that there are variations among different groups of patients.

S100B is a Ca²⁺-binding protein secreted from glial cells. It plays important roles as both an intracellular and an extracellular regulator of cell proliferation, differentiation, and survival.³³ However, an excessive release of S100B contributes to mitochondrial dysfunction and induces inflammatory-cytokine release from astrocytes and microglia, leading to neuroinflammation and apoptosis.^{34,35} In humans, high levels of serum S100B have been detected in first-episode and recurrent, unmedicated schizophrenia patients. Elevated serum S100B was also associated with a disturbed white

matter volume; this suggests cerebral dysconnectivity, a major cause of cognitive impairment.³⁶ It has been proposed that high levels of the peripheral S100B protein could be induced by glial activation.³⁷ This is also related to the increased inflammatory regulation factors and higher severity of symptoms in schizophrenia patients.³⁸ Moreover, increased serum S100B has been correlated with declines in processing speed, attention, visual learning, and reasoning/problem-solving in relapsed schizophrenia patients.³⁹ However, previous studies mentioned that a decreased S100B level could be found in medicated schizophrenia patients,^{40,41} suggesting that there are different alterations in the S100B levels among various groups of schizophrenia patients.

Although these peripheral growth factors and cytokines have been extensively studied in schizophrenia, the alterations of these proteins as well as their correlations with the cognitive functions of schizophrenia patients remain controversial among disease episodes and treatments.⁴²⁻⁴⁴ The current study aimed to investigate the serum levels of BDNF, VEGF, TNF- α , and S100B in chronic schizophrenia patients with long-term medication use. Different domains of the cognitive functions were assessed. The correlations between the serum levels of these proteins and cognitive functions were determined. The findings from this research will aid the development of potential prognostic biomarkers for cognitive impairment in schizophrenia.

2 | METHODS

2.1 | Participants

Schizophrenia subjects ($n = 41$) participated in this study. Before its commencement, its protocol was approved by the Human Research Protection Unit, Faculty of Medicine, Siriraj Hospital (MU-IRB 2015/117.03.08). The written, informed consent of the participants was obtained after the nature of the procedures was fully explained. The schizophrenia subjects were outpatients of the psychiatry center at Siriraj Hospital. Having been diagnosed with schizophrenia using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, they had been medicated for at least 1 year, with at least a 6-month follow-up. The exclusion criteria for all participants were unstable vital signs, severe mental psychotic symptoms, mental retardation, alcoholism, and substance addiction. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2 | Assessment of psychotic symptom severities

The psychotic symptom severities of the schizophrenia patients were assessed using the Clinical Global Impression–Severity scale. The severity of the illness of each patient was scored from 1 (normal) to 7 (extremely ill).

2.3 | Cognitive function test

The memory and learning functions of all 41 participants were assessed using the Logical Memory and Verbal Paired Associates subtests of the Wechsler Memory Scale–Third Edition (WMS–III).⁴⁵ The participants' processing speed and attention were evaluated with Digit Symbol-Coding, from the Wechsler Adult Intelligence Scale (WAIS–III)⁴⁵; the Trail Making Test–Part A⁴⁶; and the Stroop Color and Word Test.⁴⁷ The subjects' executive functions were assessed using the Digit Span and Letter-Number Sequencing subtests of WAIS–III⁴⁵; the Wisconsin Card Sorting Test⁴⁸; the Trail Making Test–Part B; and the Stroop Interference Test.⁴⁷ Lastly, intelligence was estimated with the Similarities and Vocabulary subtests of WAIS–III⁴⁵ (Table 2).

2.4 | Serum collection

Blood samples were collected from the 41 participants (within 24 hours before the cognitive function test) between 9 and 11 AM and transferred to non-anticoagulant tubes. The samples were allowed to clot at room temperature for 30 minutes before being centrifuged at 2000g at room temperature, for 15 minutes. The supernatants were subsequently transferred gently to 1.5-ml microcentrifuge tubes and stored at -80°C until use.

2.5 | Serum protein measurement

The levels of serum BDNF, VEGF, and S100B were measured using MILLIPLEX MAP Human Neurodegenerative Disease Magnetic Bead Panels 3 and 4 (Merck, Darmstadt, Germany). The serum TNF- α levels were quantified with MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel (Merck). Briefly, magnetic beads coated with antibodies of the proteins were mixed with the serum in black 96-well plates. Biotinylated detection antibodies were then added, followed by PE-conjugated streptavidin. After the beads were washed with washing buffer, fluorescence signals were detected using MAGPIX. Percent recovery of all standards was controlled in 70–130% range. Serum protein concentrations were quantified using a standard curve with $R^2 \geq 0.9$.

2.6 | Statistical analysis

Demographic and clinical data were analyzed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Categorical data, such as gender, were analyzed with the chi-squared test. Data were presented as mean \pm SD. The relationships between the serum protein levels and the neurocognitive scores were analyzed and represented by Pearson's correlation coefficient (r) for BDNF, TNF- α , S100B, and Spearman's rank correlation coefficient (r_s) for VEGF. P -values < 0.05 were considered significant correlation.

TABLE 1 Demographic and clinical characteristics

Variables	Schizophrenia (n = 41)
Gender: Male/Female	51.2/48.8 (%)
Age (years)	40.6 \pm 9.9
Minimum age (years)	20
Maximum age (years)	61
Years of Education (years)	12.85 \pm 3.5
Age onset (years)	25.63 \pm 7.2
Duration of illness (months)	14.97 \pm 8.3
Antipsychotics (YES/NO)	41/0
FGAs	19.5 (%)
SGAs	51.2 (%)
FGAs + SGAs	29.3 (%)
Additional drugs	87.8 (%)
Clinical Global Impression (mean \pm SD)	3.49 \pm 0.68

3 | RESULTS

3.1 | Demographic data

Table 1 the demographic and clinical characteristics of the 41 schizophrenia patients. All of the schizophrenia subjects were being treated with antipsychotics and some additional drugs (antianxiety, antidepressant, antiepileptic, antiparkinsonian, or antiseizures). The average age at onset of schizophrenia was 25.63 \pm 7.21 years, and the average duration of the illness was 14.97 \pm 8.34 years. The mean illness severity of the schizophrenia subjects (assessed with the Clinical Global Impression–Severity scale) was 3.49 \pm 0.68. This represents a mild to moderate illness.

3.2 | Associations between cognitive functions and BDNF, VEGF, TNF- α , and S100B in schizophrenia patients

Cognitive impairments are one of the core symptoms of schizophrenia. Normally, the dysfunctions arise during early psychotic episodes and persist throughout the course of the illness.⁴⁹ To evaluate the cognitive functions of the chronic schizophrenia patients, they undertook 18 tests under the supervision of psychologists. Between them, the tests measured executive functions; intelligence; and four major cognitive domains (memory and learning functions, processing speed, and attention). Each domain was divided into several cognitive function tasks. The serum levels of BDNF, VEGF, TNF- α , and S100B in the schizophrenia patients were measured using multiplex, enzyme-linked, immunosorbent assays. The correlations between the scores for the cognitive tests and the serum levels of BDNF, VEGF, TNF- α , and S100B were analyzed. The Pearson and Spearman analyses revealed specific associations between the protein levels and various cognitive functions for each group of participants (Table 2). Both BDNF and VEGF tended to have positive associations



TABLE 2 Correlation test of serum proteins and cognitive scores

Assessment	Cognitive functions test	Correlation coefficient			
		BDNF	VEGF	TNF- α	S100B
Memory and learning function	Logical memory 1 (WMS-IV)	-0.004	0.406 ^b	-0.227	-0.232
	Verbal paired associated 2 (WMS-III)	0.001	0.084 ^b	-0.107	-0.097
	Logical memory 2 (WMS-IV)	-0.027	0.275 ^b	-0.204	-0.219
	Verbal paired associated 1 (WMS-III)	-0.023	0.121 ^b	-0.238	-0.148
	Learning curve (WMS)	-0.024	0.024 ^b	-0.060	-0.175
Processing speed and attention	Trail making test A	0.107	0.002 ^b	0.358 [*]	0.046
	Wisconsin card sorting test error (WCST)	0.273	-0.029 ^b	-0.174	-0.294
	Perseveration error (WCST)	0.296	0.157 ^b	0.061	-0.336 [*]
	Conceptual level R (WCST)	0.201	-0.088 ^b	-0.166	-0.287
	Digit span (WAIS-III)	-0.146	0.036 ^b	-0.428 [*]	-0.435 [*]
	Letter-number sequencing (WAIS)	0.133	0.130 ^b	-0.128	-0.155
	Stroop interference	0.343 [*]	0.142 ^b	-0.164	-0.215
Executive function	Trail making test B	-0.194	0.144 ^b	0.123	0.035
	Digit symbol coding (WAIS-III)	0.070	0.081 ^b	-0.186	-0.096
	Stroop words	0.009	-0.123 ^b	-0.136	0.047
	Stroop color	0.105	-0.033 ^b	0.011	-0.133
Intelligence	Vocabulary (WAIS-III)	0.146	0.075 ^b	-0.066	-0.250
	Similarities (WAIS-III)	-0.068	0.059 ^b	-0.254	-0.280

*p-value <0.05.

^bSpearman's correlation.

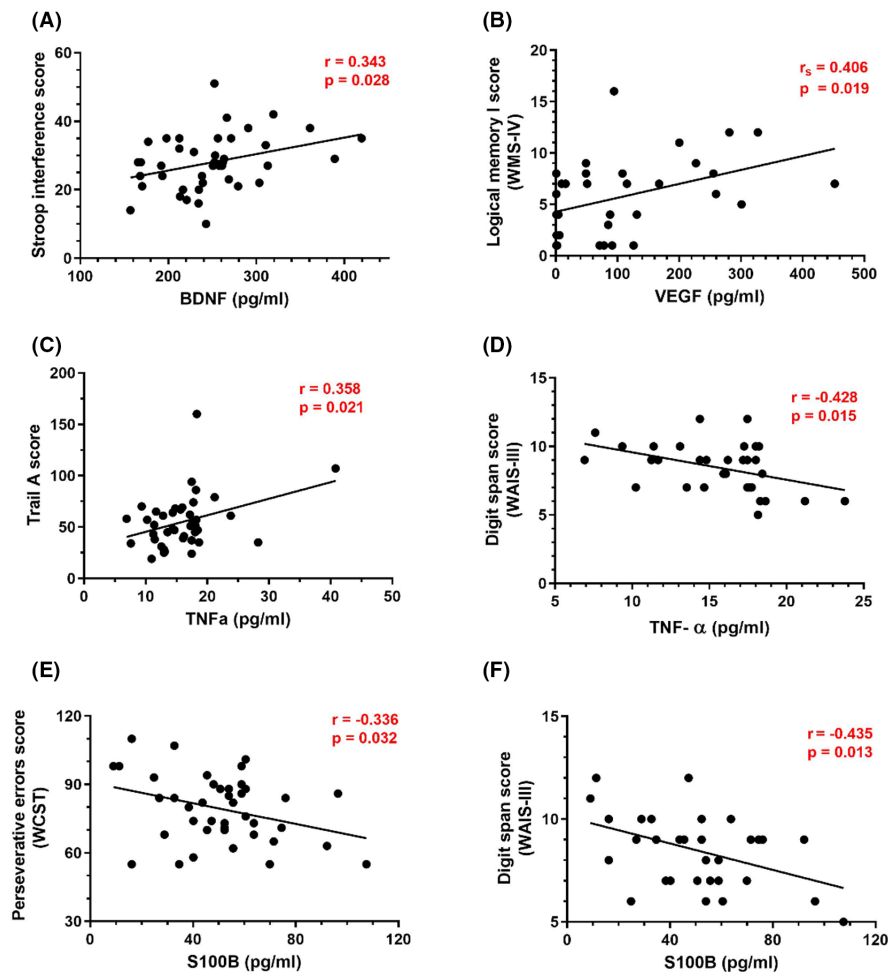
with certain tasks of cognitive functions. In the case of BDNF, its level was positively correlated with the scores of the Stroop Interference Test, which assess processing speed and attention (Figure 1A). As to serum VEGF, it was positively correlated with the Logical Memory I score (Figure 1B), which evaluates the memory and learning functions. Turning to the cytokines, TNF- α showed a positive correlation with the scores from the Trail A test (Figure 1C) and negative correlations with the scores from the Digit Span Test (WAIS-III) (Figure 1D). S100B showed negative correlations with the perseverative errors score of the Wisconsin Card Sorting Test and Digit span score (Figures 1E and F). These three tests measure processing speed and attention. Overall, the BDNF and VEGF levels tended to demonstrate positive associations with the cognitive functions of the schizophrenia patients (mainly processing speed and attention, but also memory and learning). On the other hand, the serum S100B and TNF- α levels tended to be negatively associated with the processing speed and attention of the schizophrenia patients.

4 | DISCUSSION

Our finding demonstrated that the serum levels of the BDNF, VEGF, TNF- α , and S100B proteins were correlated with the cognitive scores of medicated, Thai, schizophrenia patients. These results imply that there is an association between these proteins and brain performance in schizophrenia patients.

Generally, impairment of the cognitive functions in schizophrenia was associated with a decline in brain volume, especially a reduction in the gray matter volumes of the bilateral prefrontal cortex, bilateral hippocampus, and left superior temporal gyrus.⁵⁰ Using peripheral proteins as an indicator for cognitive functions might provide more accurate information than observing only the brain volume. From correlation analyses (Figure 1 and Table 2), VEGF was correlated with memory and learning functions, whereas BDNF, S100B, and TNF- α were correlated with processing speed and attention, which are central features of the cognitive deficits in schizophrenia.⁵¹ Both BDNF^{8,9,11,12} and VEGF⁵² have been reported for their positive associations with memory and the learning function. Recent studies have suggested that higher level of serum cytokines is associated with cognitive dysfunctions.^{44,53} In the present work, we found that both S100B and TNF- α were negatively correlated with processing speed and attention assessments in schizophrenia patients. Dysfunction in processing speed and attention has been highlighted as a central cognitive deficit. This deficit also impaired the cognitive domains of verbal memory and fluency, functional outcomes, and executive functions.⁵⁴ Taken together, multiple serum proteins might be potential prognostic biomarkers for cognitive functions, especially for schizophrenia patients. Furthermore, our findings suggest that upregulation of BDNF and VEGF coupled with downregulation of S100B and TNF- α might be targets for treatment to improve the global cognitive functions of people with schizophrenia. Future studies with drug-naive schizophrenia patients and multiple time point

FIGURE 1 Pearson and Spearman correlation analyses of the serum protein levels and the cognitive scores of the schizophrenia patients. The serum BDNF proteins correlated with the Stroop Interference Test (A). The serum VEGF proteins correlated with the Logical Memory I Test (B). Serum TNF- α correlated with Trail A Test (C). Serum S100B correlated with perseverative errors of the Wisconsin Card Sorting Test (E). Moreover, both serum TNF- α and S100B were correlated with the Digit Span (WAIS-III) Test (D and F). For all tests, lower scores signified a poorer performance, except Trail A Test which higher scores signified a poorer performance



measurements of the serum proteins are required to gain the information needed to develop prognostic markers or treatment targets for cognitive impairment in schizophrenia patients. Some limitations to this study include, firstly, the small sample size might not reflect the real tendency of all Thai schizophrenia patients. Secondly, there are confounding factors including BMI, comorbidities, type or dosage of antipsychotic treatments, and concomitant medications among subjects which might affect their cognitive functions. In addition, the genomic study should be included in the future study since BDNF gene polymorphisms and immune system gene polymorphisms seem to have an effect on cognitive functions in chronic schizophrenia.^{10,55}

AUTHOR CONTRIBUTION

P.C. and N.B. performed the experimental work and data analyses. W.R. recruited the participants. N.A. performed the cognitive function tests and data analyses. A.S. collected the blood samples from the patients. W.S., W.R., P.C., and N.B. conceived the project, designed the experiments and data analyses, and wrote the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article. The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Our data contain personal information of the participants which were not publicly available since data sharing was not included in the consent form.

ETHICAL APPROVAL

The study protocol was approved by the Human Research Protection Unit, Faculty of Medicine, Siriraj Hospital (MU-IRB 2015/117.03.08). Patient confidentiality was maintained by coding patients' files without disclosure of any private information.

CONSENT STATEMENT

After the explanation of the research procedures, all written informed consents were received from all participants.



INFORMED CONSENT

All participants provide their written informed consent.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not applicable.

ANIMAL STUDIES

Not applicable.

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