

The correlation of plasma concentration of gamma-aminobutyric acid with tactile sensory sensitivity and short sensory profile score in autistic Indonesian children

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ABSTRACT

Aim: This research was aimed to prove whether there is any relationship between plasma concentration of gamma-aminobutyric acid (GABA) and tactile sensory sensitivity and the short sensory profile (SSP) score in autistic Indonesian children. **Methods:** The participants of this research were 68 autistic children. The blood plasma of all participants was taken to determine the plasma concentration of GABA. The sensory sensitivity was examined using a touch assessment test and SSP questionnaire. All data were analyzed using a Chi-square test. **Results:** The results showed that autistic children had plasma GABA concentrations of $>0.409 \mu\text{mol/L}$ generally. However, there was no correlation shown between plasma concentration of GABA and tactile sensory sensitivity and SSP score in this research generally. **Conclusion:** This study can be concluded that there was a correlation between plasma concentration of GABA and tactile sensory.

KEY WORDS: Autism, Gamma-aminobutyric acid, Neurotransmitter, Short sensory profile, Tactile sensory

INTRODUCTION

Autism is a neurodevelopmental disorder condition in the brain, usually occurring in children, resulting in difficulties in social interaction, communication, and behavior.^[1,2] In addition, children with autism have low mental intelligence related to memory, concentration, and visual and motor coordination.^[3-5]

At present, the prevalence of autism in Indonesia is estimated at 150,000–200,000 people. This prevalence is believed to be increasing from year to year.^[6] Based on data from 2000, UNESCO declared that six out of 1000 people around the world have autism and approximately 80% are boys. Approximately one out of 88 children are identified with autism, which occurs in all racial, ethnic, and economic groups.^[7]

The cause of autism is not known at present but is thought to be multifactorial. Factors that cause autism are a combination of environmental and genetic. Genetic factors contribute to 30–40% of the occurrences of autism. In addition, children of identical twins reveal a high inheritance pattern. This indicates that the genetic component has a strong influence on the incidence of autism in children.^[8,9]

Gamma-aminobutyric acid (GABA) is the major neurotransmitter in the central nervous system.^[10] This neurotransmitter plays an important role in the embryonic period as a regulator of the balance of excitation and inhibition. GABA is produced from glutamate through an enzymatic reaction involving glutamate dicarboxylate. The dual nature of GABA is caused by the GABAergic neuron system, which is formed before the serotonergic and dopaminergic systems appear. Hence, if there is a change in the process of GABA metabolism, it might cause the GABA concentration to rise. Excess GABA concentration contributes to the pathophysiology of autism syndrome.^[20] The activity

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of GABA receptors and GABA concentration can cause some human neurodevelopmental disorders that play an important role in the incidence of autism in both humans and animals.^[11-13] GABA inhibits nerve transmission in the brain by inducing GABA receptors, causing postsynaptic membrane hyperpolarization and produces autism symptoms.^[14,15]

GABA receptor genes are known to be associated closely with tactile sensory sensitivity. The tactile sensory system is set up by receptors in the skin known as touch response receptors. DeLorey *et al.* demonstrated that variability in tactile sensory sensitivity is associated with a change in the function of GABA.^[16] In addition, magnetic resonance spectroscopy studies in humans also state that impaired tactile sensory sensitivity thresholds are associated with the various concentration of GABA in the sensorimotor cortex.^[17] The tactile sensory response can be measured directly using touch and can also be measured using a parent-report tactile subscale of the questionnaire Short Sensory Profile (SSP). SSP is a method of measuring sensory system response using a questionnaire. Usually used to determine the contribution of the sensory aspects of children in everyday life, it can be used in the study of autism syndrome to explain the difference in tactile sensitivity.^[18,19] This study aims to investigate the correlation between the concentration of GABA and changes in the tactile sensory sensitivity, as well as the SSP questionnaire score in autistic Indonesian children.

MATERIALS AND METHODS

Research Subject

The participants of this study were 68 autistic children aged 6–13 years old who lived with their parents. The participants were recruited from the Center for Autism Services, Extraordinary Schools, and Inclusion Elementary School in Malang. This study has received approval from the Research Ethics Committee of the Faculty of Medicine, Brawijaya University, Indonesia No. 502/EC/KEPK/09/2015.

Research Design

This type of research was a case–control study with an epidemiological approach to determine the correlation between the concentration of GABA and changes in tactile sensory sensitivity in autistic Indonesian children. All participants were asked for consent and screen through their parents, before the research.

Blood Sampling and Measurement of GABA Concentration

Plasma samples were obtained from about 3 mL of blood samples taken from a vein. The blood was placed into a vacutainer and then allowed to stand for 1 h, then centrifuged at 3000 rpm for 7 min to

obtain a supernatant. Measurement of GABA was by a sandwich enzyme-linked immunosorbent assay (ELISA) (Elabscience, Biotechnology, Wuhan). Standard and plasma samples obtained were put on a microtiter plate with a specific antibody and incubated at 37°C for 2 h, then added to the specific antibody biotinylated detection of 100 mL and incubated 37°C for 1 h. Afterward, the streptavidin-horseradish peroxidase conjugate was added to each microplate sample of 100 mL and incubated at 37°C for 30 min. The addition of 100 mL 3,3',5,5'-Tetramethylbenzidine (TMB) substrate solution followed, then incubated for 30 min at room temperature. The last addition was 100 mL stop solution (HCl) conducted in a dark room until its color changed. The reading of the results of optical density using an ELISA reader at a wavelength of 450 nm. Hormone concentrations in the samples were calculated by comparing the OD score against a standard curve.

Tactile Sensitivity Measurement

Tactile sensory sensitivity was measured using two methods: Touch assessment test and SSP questionnaires. The touch assessment test (touch assessment test) is to touch and scratch the skin of the blindfolded participants' arm for 1.5 s. Then, the participants were asked to say where they felt the stimulus touches, chosen randomly. Touch assessment tests were used in this study to examine the tactile sensitivity response to touch and pain.

The SSP questionnaires given and filled in by caregivers, consisted of 38 questions to discover the sensory experience in the daily lives of the children. SSP questionnaires use a tactile scale score, where parents were asked to describe their child's behavior according to SSP items.^[19]

Statistical Analysis

The data obtained were tabulated and analyzed. The data sample characteristics in general and GABA concentrations were analyzed with descriptive statistics. Relationship between plasma GABA concentration and impaired tactile touch (tactile and pain response), and the SSP categories were analyzed using a Chi-square test. The entire analysis used the statistical program SPSS for Windows, Version 17.0.

RESULTS

General Characteristic of Participants

The subjects in this study were 68 children with autism. About 47.1% (32) of the participants were in the group aged 9–11 years old and 75% (51) of them were male. The most recent levels of education of the children's parents were graduated from elementary school, junior high school, and D3-S2. Almost all participants' fathers worked (66 men, 97.1%). The

results of the calculation of the characteristics of participants who completed the study are presented in Table 1.

Gaba Concentration of Participants

Plasma GABA concentration of participants, in general, appear in Table 2. The number of children with autism whose GABA concentration >0.409 mol/L was 39 (57.4%); compared to 29 children (42.6%) with autism whose GABA concentration was < 0.409 mol/L.

Relationship Between Plasma GABA and Tactile Sensory Sensitivity

The relationship between the plasma GABA concentration and tactile sensory sensitivity category of touch and pain was analyzed using statistical Chi-square test. Statistical test results between plasma GABA concentration and tactile sensory touch category showed no significant correlation ($P = 0.652$). The results of the statistical test between plasma GABA concentration and tactile sensory pain

category had a significant correlation ($p = 0.048$) with the positive score ($r = 6.070$) [Table 3].

Relationship Between Plasma GABA Concentration and SSP Category of “Always” Response

The relationship between plasma GABA concentration and SSP category of “Always” response score was analyzed using statistical Chi-square test. Statistical analysis showed no significant correlation ($P = 0.715$) between the concentration of GABA and the SSP category of “Always” response [Table 4].

DISCUSSION

We found in this study that plasma GABA concentration did not affect tactile sensory touch or SSP score. However, there was a significant correlation between plasma concentration of GABA and tactile sensory pain. This is in accordance with the research of Ashburner *et al.*, who stated that the results of SSP in autistic children of school age had a negative correlation with hyperactivity/attention.^[20] In fact, the research of Ben-Sasson *et al.* found that Autism spectrum disorder (ASD) toddlers were mostly characterized by under-responsiveness and stimulus avoidance, with a low frequency of sensation-seeking behaviors.^[21] Furthermore, the researchers asserted that stimulus-avoiding response was not strongly associated with the hypersensitivity often characteristic of ASD children. Each group had an ASD response sensitivity varying depending on the age, symptom severity, and level of intelligence.^[22] This is different from the latest research reports of over-responsiveness, tactile parent-reports of symptoms and self-reports of pleasantness to textures in children with ASD. The results of these studies indicated that ASD children were significantly more sensitive/over-responsive compared to the controls. There was also a correlation between over-responsiveness with the tactile result from parental reports.^[23]

ASD is characterized by a disturbance in the process of organizing primary tactile senses. Tactile stimuli from the environment are recorded and interpreted in the brain or central nervous system. The sensation would then affect the movement or motor response, which, in turn, is feedback into the brain. Disturbances and problems in ASD in processing sensory input cause the ASD child to give an inconsistent response to the stimulation received, often to fail to process important information and to be prone to stress and anxiety.^[24,25] Until now, the neurobiological mechanism of the abnormal incidence of the tactile system and symptoms of ASD are still not known clearly and definitely. These abnormalities may be exacerbated due to the dysfunction in the excitation/inhibition balance of the central nervous system of children with ASD. Any inconsistencies or differences in the results of several studies of tactile

Table 1: General characteristics of participants research

Categories	Total n (%)
Age (years)	
6–8	23 (33.8)
9–11	32 (47.2)
≥ 12	13 (19.0)
Gender	
Male	51 (75.0)
Female	17 (25.0)
Father education background	
No education/non-graduated primary school	1 (1.5)
Graduated from primary school/junior high school	17 (25.0)
Graduated from high school	32 (47.1)
Graduated from college (diploma/bachelor/master)	18 (26.4)
Mother education background	
No education/non-graduated primary school	1 (1.5)
Graduated from primary school/junior high school	22 (32.4)
Graduated from high school	24 (35.3)
Graduated from college (diploma/bachelor/master)	21 (30.8)
Fathers' occupation	
Not working	2 (2.9)
Working	66 (97.1)
Mothers' occupation	
Not working	42 (62.8)
Working	26 (38.3)

Table 2: Participants' GABA level

GABA level	Total n (%)
<0.409 $\mu\text{mol/L}$	29 (42.6)
>0.409 $\mu\text{mol/L}$	39 (57.4)

GABA: Gamma-aminobutyric acid

Table 3: The relation of GABA plasma levels with tactile sensory

Tactile sensory	GABA level		Total <i>n</i> (%)	Chi-square test	
	<0.409 $\mu\text{mol/L}$	>0.409 $\mu\text{mol/L}$		<i>r</i>	<i>p</i>
	<i>n</i> (%)	<i>n</i> (%)			
Touch					
Idle	5 (55.6)	4 (44.4)	9 (100.0)	0.857	0.652
Sensitive	16 (39.0)	25 (61.0)	41 (100.0)		
Sensitive optimal	8 (44.4)	10 (55.6)	18 (100.0)		
Sore					
Idle	4 (100.0)	0 (0.0)	4 (100.0)	6.070	0.048*
Sensitive	16 (42.1)	22 (57.9)	38 (100.0)		
Sensitive optimal	9 (34.6)	17 (65.4)	26 (100.0)		

*Within a row scores with different superscripts are significantly different. $P < 0.05$, $n = 68$. GABA: Gamma-aminobutyric acid

Table 4: Plasma levels of GABA relationship with SSP score category response “always”

SSP	GABA level		Total <i>n</i> (%)	Chi-square test	
	<0.409 $\mu\text{mol/L}$	>0.409 $\mu\text{mol/L}$		<i>r</i>	<i>p</i>
	<i>n</i> (%)	<i>n</i> (%)			
Response “always”					
≤ 10	11 (40.7)	16 (59.3)	27	100.0	0.672
11–20	14 (41.2)	20 (58.8)	34		
21–30	4 (57.1)	3 (42.9)	7		

*Within a row, scores with different superscripts are significantly different. $P < 0.05$, $n = 68$. GABA: Gamma-aminobutyric acid, SSP: Short Sensory Profile

processing in ASD children with respect to patterns of response, especially with respect to over- and under-sensitive, are likely to result from the subjectivity of clinical assessments, the heterogeneity of ASD cohorts (age, symptom severity, and level of intelligence), and the diversity of tactile sensitivity measures.^[26]

CONCLUSION

The absence of a significant correlation between the concentration of GABA with tactile sensory sensitivity and the score of SSP was likely to be due to the different characteristics of the ASD group and methods of measurement.

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