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Measuring motor evoked-potentials in children with autism spectrum disorders accompanied with cerebral vein thrombosis following intraarterial heparin flushing



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ABSTRACT

Background: The use of the term “Autism Spectrum Disorder” has led to confusion over this substance. Prior to DSM-V criteria, symptoms of Autism Spectrum Disorder (ASD) refers to the problems in brain vasculature and brain chemistry most likely affect the children behavior, whereas the authors’ findings suggest such problems depicting a similar anomaly in cerebral vein thrombosis case (CVT). Recently, the evoked potentials, that demonstrated in CVT, have a possible prognostic value on patients suffering from ASD. This study purposes to measure the motor evoked potentials (MEPs) on patients following the intervention of intraarterial

heparin flushing (IAHF).

Methods: A descriptive study was conducted on 17 patients admitted in Cerebrovascular Center of RSPAD Gatot Soebroto, Jakarta, diagnosed with ASD presenting CVT. The MEPs value was measured by conforming the IAHF procedure.

Results: The MEPs value (amplitude, latency, CMCT) pre and post-IAHF showed an increasing value. Meanwhile, there was a lowering value of latency and CMCT in left cortical participants after IAHF.

Conclusion: The group tends to perform more expected positive MEPs changes after IAHF.

Keywords: MEPs, ASD, CVT, IAHF, amplitude, latency, CMCT

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INTRODUCTION

Autism Spectrum Disorders (ASD) is long well known and defined as a neurodevelopmental disorder, which the disease is characterized by a widespread of abnormalities in social interactions, communication, and limited interests with highly repetitive behaviour.¹ Considering its wide array of symptoms manifesting as neuronal disruption, several authors thought autism as a disorder of neural connectivity.² autism was termed as a pervasive developmental disorder, where the presentation was necessary prior to 30-month-old, with the presenting symptoms and signs consists of lack of interest in people, gross impairment in communication, and uncommon responses to environmental stimulation and interactions.⁵ These conditions are suggested to be present at birth and are diagnosable by 18 months of age. Nowadays, the known ASD case recorded by The Centres for Disease Control and Prevention currently estimates the prevalence rate of Autism Spectrum Disorder (ASD) in the United States alone is approximately 1 of 88 children (1 of 54 boys and 1 of 252 girls)⁷ while the male to female sex ratio is 4:1.⁸ Most of the children

diagnosed with autism how sensory and perceptual abnormalities. They have both hyposensitivity and hypersensitivity to sensory, auditory, and visual stimuli.⁹ Besides the known disturbance in sensory and perceptual aspect, there is also gait problems that commonly found in children with ASD which confirmed by the qualitative rating of “body use” on the Childhood Autism Rating Scale (CARS), related to the motor dysfunction. However, when Magnetic Resonance Imaging (MRI) examination was performed on children who suffer from ASD such as poor concentration, repetitive movement and lack of communication, the results showed that there were signs of CVT. Study of de Veber et al. showed that the signs and symptoms of CVT in pediatric patients may differ, but the typical clinical features are seizures, headache, respiratory distress, and focal neurological deficits.⁷ Patients whose diagnosed with CVT may also present with deficits related to venous infarction which ranging from developmental delays, learning disabilities, hemiparesis, and hemisensory loss.^{7,90}

As the theory of Excitatory-Inhibitory (E-I) imbalance is one of the possible etiology of ASD, one of the known likely causative is

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increased glutamatergic or decreased signaling in GABAergic. Couples of examination tools such as electroencephalogram (EEG) and magnetoencephalography (MEG) possibly can be used to determine the E-I imbalance in ASD alone, or together with Trans Magnetic Stimulation (TMS) which can provide useful biomarkers and outcome measures.⁵³ Since E-I imbalance is under the scope of neurophysiology, measured by a particular tool is needed. Thus, it used motor evoked potentials (MEPs) which measured by TMS method. According to American Clinical Neurophysiology Society, MEPs are a collection of electrical signals recorded from neural tissue or muscle using a particular tools and techniques following the activation of central motor pathways which also act as a complement to another clinical neurophysiology techniques, for example is somatosensory evoked potentials (SEPs), considering the assessment of the human nervous system. TMS can also be used to investigate cortical and cortico-spinal plasticity mechanisms in a non-invasive way. These mechanisms have also been implicated in the ASD pathophysiology.^{27,28}

There are few treatment strategies for ASD presenting with CVT cases in children, but most children receive anticoagulation regimens. The delivery method of anticoagulants therapy may vary between centers. In RSPAD Gatot Soebroto Jakarta, Digital Subtraction Angiography (DSA) method was used both as a diagnostic tool and a therapeutic method after modified by Terawan et al.⁹³ A modified DSA procedure was a method of delivering anticoagulation therapy directly to the occluded vessels guided by imaging technique in further called IAHF (IntraArterial Heparin Flushing), where the only difference between IAHF and the original DSA was the continuous directed local flushing of heparin into the occluded vessels.⁹⁰ There is still limited literature discussing ASD presenting with CVT and IAHF. Thus, this study suggests the motor evoked potentials (MEPs) as the investigation tools because it is well understood that MEPs were directly correlated with the motor performance itself, or accuracy of movement.¹⁸⁻²⁰

METHOD

The participants of this study were obtained from Cerebrovascular Center of RSPAD Gatot Soebroto, Jakarta, who registered as patients that admitted by the pediatricians, then consulted to a group of medical specialties consist of Psychiatrist, Neurologist, Physiatrist, and Interventional Radiologist. All participants, which obtained from their parents, gave their informed written consent before being tested. The procedure was approved by the Cerebrovascular Center of RSPAD Gatot

Soebroto, Jakarta. The methods carried out in this study are in accordance with approved guidelines.

Participants were tested in a sitting position with forearm supported in a pronated position. A standard skin preparation⁹² procedure was performed for each electrode placement site. EMG electrodes were placed on the first dorsal interosseous (FDI) muscle of the dominant hand. MEPs size measurement was performed by using TMS Neurosoft Variant 4 (Neurosoft, Ivanovo, Russia). Big ring coil was placed on the vertex, and a single pulse stimulation was given. Side B of the coil (anticlockwise) was used to stimulate left hemisphere, while side A (clockwise) to stimulate right hemisphere. To measure latency (millisecond/ms), amplitude (millivolt/mV), and CMCT (ms), the MEPs value was recorded with stimulation of submaximal threshold 80% MEP at each side. The MEPs value was measured both pre-IAHF and 4 hours post-IAHF procedure.

RESULTS

Seventeen participants with ASD (11 males; aged 6-16 years old) took part in this study. The participants were measured for the MEP results before and 4 hours after the IAHF procedure (as seen in Table 1).

Table 1 shows the difference between MEPs value pre and post-IAHF procedure. All the MEPs value seems to be increased both in left and right cortical. In the right cortical, the average MEP amplitude value has increased 0.3 point while the latency value has increased as much as 2.344 point. It's also shown at CMCT value, which has increased 0.72 point. Meanwhile, in the left cortical, the average amplitude value has increased as much as 0.757 point while the latency value and CMCT values also increased as much as 0.78 and 0.27 point, respectively.

As shown in Table 2, there was a significant difference to be noticed in its value on participants' MEP in both hands post-IAHF. Amplitude and CMCT value of MEPs in the right cortical were increased, while the latency value was decreased. On the other hand, the amplitude of MEPs in the left cortical was significantly decreased, while the latency and CMCT value of MEPs was slightly increased.

DISCUSSION

Children age group which ranges from 6 to 16 years was suffered from Autism Spectrum Disorder (ASD). The patients passed some essential examination from several specialties such as Pediatrician, Psychiatrist, Neurologist, and also

Table 1. General MEPs Value pre and post-IAHF procedure

Variables (n=17)	Pre-IAHF	Post-IAHF	Δ
Left hand (μ)			
Amplitude	0.60	0.9	0.3
Latency	17.8	20.133	2.344
CMCT	8.203	8.92	0.72
Right hand (μ)			
Amplitude	0.7	1.474	0.757
Latency	17.089	17.87	0.78
CMCT	7.56	7.82	0.27

Table 2. MEP Results in Right and Left-cortical post-IAHF

Variables (n=17)	Right Cortical			Left Cortical		
	Amplitude	Latency	CMCT	Amplitude	Latency	CMCT
Increased	8 (47%)	10 (58%)	7 (41%)	12 (70%)	7 (41%)	8 (47%)
Decreased	9 (52%)	7 (41%)	10 (58%)	5 (29%)	10 (58%)	9 (52%)

Intervention Radiologist to make sure the patient condition is suitable for this procedure and make sure the safety of the patient. Numerous studies already reported that there was a possibility of motor deficits that might coexist in individuals with ASD, including alterations in motor milestone development⁴⁶, clumsiness, motor incoordination, disturbances in reach-to-grasp movement⁶⁴⁻⁸⁶, deficits in gross and fine motor movement⁸⁷, and also impaired postural control.¹⁶⁻⁸⁸ Once after MEPs value was obtained, further examination such as Magnetic Resonance Imaging (MRI) was needed. Problems in brain anatomy development as a causative factor in ASD is also possible, and based on the experience in RSPAD, most of children suffered from ASD will most likely have abnormality in their brain vasculature, therefore the MRI which include Magnetic Resonance Venography (MRV) and Magnetic Resonance Perfusion (MRP) is performed. However, the abnormality in brain vasculature also found in Cerebral Vein Thrombosis (CVT) cases in pediatric patients. CVT diagnosis was established by an anticoagulant therapy with catheter guide help using a digital imaging technique called Digital Subtraction Angiography (DSA), which has been developed and modified by Interventional Radiologist team in RSPAD Gatot Soebroto, Terawan, now specifically called Intraarterial Heparin Flushing (IAHF).⁹⁰ This supported by the findings in de Veber study. When MRI examination was performed on children who suffer from symptoms resembled an ASD such as

poor concentration, repetitive movement, and lack of communication, the results showed that there were signs of CVT. The sign and symptoms of CVT in pediatric children may vary, but most common clinical features are seizures, headache, respiratory distress, and focal neurological deficits.⁹¹

In general population of this study, there was no significant difference in MEP values pre and post-IAHF procedure, but there were some significant differences in amplitude, latency, and CMCT when the results were categorized into left and right-cortical post-IAHF, which possibly showed a typical positive outcome in left cortical participants, seemed to depict a motor recovery and improvement in these participants' clinical condition. This improvement was measured by the psychiatrist using Childhood Autism Rating Scale (CARS) and also from the patient parents or legal guardians testimony, which described such more positive changes in patient behavioral status.

CONCLUSION

The group tends to perform more expected positive MEPs changes after IAHF.

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ETHICAL CLEARANCE

Ethical Committee of RSPAD Gatot Soebroto.

CONFLICT OF INTERESTS

The authors declare that there were no conflicts of interest in the process of this study.

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AUTHOR CONTRIBUTION

All of authors are equally contributed to the study from the study framework, data gathering, data analysis, until reporting the result of study.

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