Utilization of modified digital subtraction angiography in a child with cerebral venous sinus thrombosis presenting with autism spectrum disorder symptoms: A novel approach

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ABSTRACT

Background: The limited number of case reports about Cerebral Venous Sinus Thrombosis (CVST), especially in the pediatric population who also present with Autism Spectrum Disorders (ASD) symptoms, prompted the authors to be the pioneer in reporting of pediatric CVST with ASD symptoms case in Indonesia. In this study, we would like to report a case of an 8-year-old patient with ASD who was diagnosed with CVST after undergoing Magnetic Resonance Imaging (MRI) examination. After the diagnosis was established, the patient underwent a modified Digital Subtraction Angiography (DSA) method, which was later termed as Intra Arterial Heparin Flushing (IAHF) as its treatment option.

Case presentation: An 8-year-old-boy was brought by his parents to Gatot Soebroto Hospital with speech and communication problems, and also cognitive and behavioral problems such as the inability to count, read words, follow orders and maintain emotional stability. After a thorough standard examination by the attending physician, further examination using Magnetic Resonance Imaging with MR perfusion was suggested to establish a diagnosis. The imaging results showed a decrease in blood flow in the transverse sinus and straight sinus, and also in the internal jugular vein. The patient was diagnosed with CVST. The patient underwent anticoagulation therapy, which was administered through a modified DSA method, which was later termed as IAHF procedure, to increase the cerebral blood flow.

Conclusion: After the patient underwent the IAHF procedure, good clinical outcomes were immediately seen, even at six months follow up. The parents reported that there were improvements in the patient’s cognitive and behavioral status.

Keywords: autism spectrum disorder, cerebral venous sinus thrombosis, digital subtraction angiography, intra arterial heparin flushing

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INTRODUCTION

Currently, Autism Spectrum Disorder (ASD) is widely known as a complex problem, which is primarily found in children. We would like to report a case of a child who suffers from ASD symptoms since he was 18 months old. This case was interesting because brain Magnetic Resonance Imaging (MRI) examination showed decreased blood flow in the internal jugular vein, transverse and straight sinus, which was concluded as Cerebral Venous Sinus Thrombosis (CVST). This case may provide more insight into the possibility of CVST that could lead to ASD presentation in pediatric patients since CVST with ASD presentation is rarely reported, especially in Indonesia.

The incidence rate of CVST in the pediatric population is 0.67 per 100,000 children per year.3 The reported incidence rate is 0.34 per 100,000 children per year when neonates are excluded.4 The clinical presentation in neonates is usually seizures or lethargy, while in older infants and children (similar to adults), the common presentations are seizures, altered levels of consciousness, headache with papilledema, isolated intracranial hypertension, or focal neurological deficits.

The known etiology of CVST in the pediatric population varies. In neonates, it could be caused by acute systemic illnesses such as shock or dehydration. However, in older children, local infection such as mastoiditis and coagulopathy could be the cause of CVST. In older children and adolescents, systemic lupus erythematosus, nephrotic syndrome, leukemia or lymphoma with 1-asparaginase treatment, and trauma have been reported as causes of CVST.34 Iron deficiency anemia is also an established risk factor for CVST.

Unlike adult CVST, long-term outcomes of neonatal CVST have been estimated to be severe with disabilities. The possibility of CVST as a predisposing risk factor for the developmental delay might be considered as up to 58% of patients had developmental delay, 28% had cerebral palsy,
and 20% had long-term seizure disorders.8

Pediatric CVST usually affects a single sinus. Huisman et al.9 found that the superior sagittal sinus or transverse sinuses were involved in 47.5% and 12% of cases, respectively. In the same study, the involvement of two sinuses was seen in 30% of the cases. Transverse sinus thrombosis was more common (73%) than sagittal sinus thrombosis (35%).10 In this case, the thrombosis was found in the transverse and straight sinus.

The treatment strategy of CVST is based on symptomatic and supportive measures. Most patients are treated with hydration and/or antibiotics. The anticoagulation is less commonly used especially in neonates. Surgical treatment is usually indicated for patients with hydrocephalus or intracerebral hematomas. The American Heart Association recommends antithrombotic therapy in neonates with severe thrombophilic disorders, multiple emboli (cerebral or systemic), or propagating CVST.8 Anticoagulation administration can be delivered either by intravenous unfractionated heparin or subcutaneous administration of low molecular weight heparin. They can be established as mediator before oral anticoagulation with vitamin K antagonist. Anticoagulation treatment with low molecular heparin and warfarin are considered safer in children with CVST.11

In this case, the anticoagulant treatment was unfractionated heparin which was delivered directly to the thrombus site using a catheter. The catheter was directed with the guidance of digital subtraction angiography, which was already modified as IAHF. The objective of this procedure was not only for diagnostic but also for therapeutic goals. After the IAHF procedure was performed, no adverse event occurred even at six months follow up. The expected adverse events such as hematomas, bleeding or focal neurological defects were not found in this patient.

**CASE PRESENTATION**

We present a case of an 8-year-old Vietnamese male patient who was brought by his parents into the hospital to receive further treatment for their child’s condition. The child was diagnosed with ASD and treatment showed a slow response. There were no visible favorable outcomes. As a result, the parents tried to seek a second opinion in Indonesia, in particular at RSPAD Gatot Soebroto, Jakarta. The parents reported that the patient struggled with some sensory issues (tactile, vestibular, and proprioceptive). He had a low attention span, ineffective movement coordination, and could only speak 3 or 4-word phrases, which were unspontaneous repeated phrases. The parents also tried to teach the alphabetic words and numbers to the patient since he was four years old. However, the result was not satisfying. The patient had a tantrum, which manifested in him hitting his head. It was suspected that the patient might suffer from headaches but was unable to express his condition due to his limited ability to communicate.

The patient was handled by the Autism Team at RSPAD, which consisted of four professional medical specialists (neuropediatrician, psychiatrist, interventional radiologist, and physiatrist). The patient underwent standard examinations, which included physical examination, laboratory tests (complete blood count, coagulation profile, electrolytes, and chemical profile) and psychiatric screening. The laboratory tests showed no abnormalities according to standard laboratory values.

The psychiatrist performed a DSM mental status examination and the Childhood Autism Rating Scale (CARS), which showed moderate autism. Five diagnostic axes by DSM-IV-TRE was performed by a psychiatrist to assess the mental status of the patient. Axis 1 showed moderate autistic, while axis 2 and 3 showed no results. Axis 4 showed cognitive and behavioral developmental problems and axis 5 showed a Global Assessment of Functioning (GAF) score of 40-50. The psychiatrist also measured the CARS score. CARS is a 15-item observation-based rating scale that yields a total score reflective of autism symptom severity. CARS scores range from 20.0 to 48.5, and our patient’s score was 44, which indicated moderately autistic. A similar result was found in a study by Moulton, where the average CARS score was 32.42 (SD = 5.19), which fell into the “mild to moderate autism” range based on the original CARS cutoff.1

MRI examination with Magnetic Resonance
the brain. This typical finding in MR perfusion is quite commonly found in children with an autistic presentation in Gatot Soebroto hospital. The authors called these typical findings as the "ring of fire" (Figure 3).

Based on these findings, the interventional radiologist suggested a further treatment choice to IAHF. IAHF procedure itself was an already known as DSA method but modified by Terawan, where it was not only used as a diagnostic tool but also a therapeutic method called IAHF. It is an anticoagulation therapy using unfractionated heparin delivered to the site of occlusion directly through a catheter. After the parents received all the information about the problem, procedure, and expected adverse events, the consent was given to the parents to be signed as a form of affirmation. After the parents signed the informed consent, the patient underwent all the necessary examination to make sure the patient was in a safe environment from the beginning to the end of the procedure.

The patient was received general anesthesia to prevent any unnecessary movements that might affect the quality of the procedure. The patient was disinfected using povidone iodine 7.5%, and alcohol 70% and the puncture area was isolated with sterile drapes. The catheter, sheath catheter, introducer, guide wire, lidocaine in a disposable syringe, the mixture of 5000 IU of unfractionated heparin in 500cc saline were prepared before the procedure. The procedure started by puncturing of the femoral artery with 18G abocath and inserting the short guide wire into the abocath. Fluoroscopy was performed to establish the correct position. Abocath was released, and the introducer sheath was inserted. The introducer sheath cap and guide wire were pulled at the same time. Heparin flushing was performed until the sheath was clean. Angiography catheter was inserted with the guidance of a long guide wire until it reached the carotid artery and the guide wire was pulled and released. Angiography was done with contrast medium, and heparin flushing was performed in both carotid artery and vertebral artery. After the procedure was completed, the catheter was released with the guidance of the guide wire, and the sheath was released. The bleeding in the femoral artery was stopped using a conventional method such as an angiographic sandbag or using a closure device. The procedure was completed in 30 minutes and the patient was brought to the infirmary to rest for 4 hours.

In this case, we can see from both of the MRV of the patient that the density of transverse and straight sinus plus the internal jugular vein increased after the IAHF procedure. These findings
the procedure, he would have just stayed in bed and urinated on his bed. Since undergoing the procedure, the patient no longer needs to wear a diaper at night. The parents also reported that the patient started to like trying new food on the plane on their way back home and he now can eat various kinds of food and wants to try new things, which were not evident before the patient underwent the IAHF procedure. The patient was discharged from the hospital as no adverse events occurred.

According to the parents, three weeks after the IAHF procedure, the patient could understand numbers 1 to 5 and then from 10 until 100; the patient could already learn to count. Six months after the IAHF procedure, the patient managed to learn new words and could read about 30 words related to his activities and his family member’s activities in the morning. In terms of clinical assessment, this patient’s CARS score showed better outcomes. Twelve months after the procedure, the CARS for this patient was measured again, and the result was 31, which indicated the mildly moderate autistic category.

An improvement in motor coordination was found in this patient. The patient had better observation and imitation skills (gross and fine motor skills). The patient was more cooperative in class, during intervention sessions, and in family activities. His engagement and social interaction had greatly improved when he wanted to interact and initiate interaction by both verbal and gesture with adults and peers. The parents also reported that the development of the patient’s cognition has also improved.

After ten months, another MR perfusion was performed on the patient, and the results showed a more equally distributed blood perfusion (Figure 5). These typical changes in MR perfusion were also accompanied by clinical improvements in the patient’s condition. Based on these clinical and imaging findings, the authors suggest that these typical MR perfusion result might become a new standard value of improvement of CVST in pediatric populations especially with those with autism symptoms presentation.

DISCUSSION

Patients who suffer from CVST do not usually have any specific clinical complaints, especially in the pediatric population since they still have limited communication skills. In this case, the patient had ASD with typical CVST imaging findings, which is quite intriguing. This report might suggest that CVST could be a possible etiology for ASD.

As mentioned above the correlation between imaging findings on this patient that suffered
Figure 4. MRV after IAHF

Figure 5. MR perfusion after IAHF

from ASD symptoms has the same profile in those who suffer from CVST. The MRV result showed a decreased blood flow in the right transverse sinus and straight sinus. These findings coincide with the study from Maguire, et al. that described the transverse sinus thrombosis was more common (73%) than sagittal sinus thrombosis (35%). These findings might suggest that such condition like CVST can also affect the patient brain developmental status even though this patient did not quite show common classical symptoms of CVST in children as mentioned above. However, based on these imaging findings, we might discover a new possibility of CVST relation with ASD symptoms. As mentioned above by de Veber, et al., long term outcomes of neonatal CVST may cause developmental delay. Also as shown in Figure 6 below, a thrombosis in straight sinus can manifest as mental status changes in the patient condition.

After the diagnosis was established, further treatment strategies were decided for this patient. In this case, the treatment of choice was anticoagulation therapy which delivered directly into the patient brain vasculature using catheterization with digital Subtraction angiography method which in this case was modified and termed as intra-arterial heparin flushing. The reasons for anticoagulation therapy in thrombosis cases are to prevent thrombus propagation, recanalize occluded sinuses and cerebral veins, and prevent complications of deep vein thrombosis and pulmonary embolism.

After undergoing the therapy, the patient's clinical condition improved. The improvements suggest that fixing the problems in brain vasculature most likely might improve the patient clinical condition who suffers from ASD. The authors realize that further study still needs to be done such as longer follow up to give us more insights into how this therapeutic strategy could maintain the improved clinical condition of patients with the same condition.

The author believes that these phenomena might indicate that if there are any obstructions in the venous vasculature of the brain, the homeostatic response increases angiogenesis to form collateral bridges to compensate the obstruction, so the brain remains served. According to Carmeliet P., the known stimulus for the expansion of the vascular bed was hypoxia. Hypothetically, when the occlusion was released after IAHF procedure, the blood supplies did not need the collateral vessel again to reach the brain tissues since the main vessels have already been released from occlusion. Therefore, the collateral vessels no longer appear dense in the MRV findings after the IAHF procedure.
CONCLUSION
In this study, the authors found that CVST should be considered in patients with ASD presentation. When suspected, imaging examination should be conducted for further diagnosis establishment. In this case, after the IAHF procedure was performed, good clinical outcomes were reported by the patient’s parents. This study has some limitation such as the timeline of follow up. The authors hope that other studies will be conducted in the future to see if there is more after effect with a longer period of follow up time.

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CONFLICTS OF INTEREST
The authors declare that there are no competing interests in this report.

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