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The effect of intraarterial heparin flushing to autism symptoms when used to treat the concomitant cerebral venous thrombosis: a case series



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ABSTRACT

Introduction: There are still no definite therapeutic strategies for Autism Spectrum Disorder (ASD) other than behavioural interventions and few FDA approved behaviour control drugs. In this study, we found a co-existence medical condition of ASD & Cerebral Vein Thrombosis (CVT) in the paediatric population. Based on these findings, a new therapeutic approach, a catheter-directed anticoagulant therapy termed as IAHF (Intra Arterial Heparin Flushing) was performed on this population of patients.

Methods: This paper aims to describe a series of 10 cases of IAHF procedure performed to treat CVT on children with ASD from 2018 through 2019 at Cerebrovascular Center RSPAD Gatot Soebroto Jakarta-Indonesia. The children diagnosed with ASD by the multidisciplinary team but also had CVT findings on their brain magnetic resonance imaging studies when performed as the series

of comprehensive diagnostic examination. IAHF were conducted by delivering heparin through a modified DSA technique into the occluded vessels. Subject Autism status was assessed with the Childhood Autism Rating Scale (CARS) before and one month after IAHF procedures.

Results: The measurement of CARS Score after IAHF shows a relatively positive result. Eight patients showed a decreased in total CARS Score after the procedure, while only two patients had no improvement. One subject shows a decrease of nine points, the most significant changes, and improved the status from moderate to mild autism.

Conclusion: In children who have ASD and also accompanied by CVT findings in their imaging studies, IAHF treatment showed clinical improvement of the autism symptoms.

Keywords: Childhood Autism Rating Scale, Autism Spectrum Disorder, Cerebral Venous Thrombosis, Intraarterial heparin flushing

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INTRODUCTION

Autism is a well-known term for a particular behaviour impairment in the paediatric population. The very first time the term “autism” was initially introduced by Bleuler in 1911, while he studied Schizophrenia. He defined autism as a detachment from reality by way of social withdrawal or lack of a special-relation.¹ Even though Bleuler already described the term autism, but it was Leo Kanner who defined the condition in 1943 based on his observations to a group of children with peculiar behaviour characterised by innate incapacity to establish an affective and interpersonal contact with their surroundings.² Meanwhile, in India, the history of autism dates back to as early as in 1943 when Ronald, a Viennese paediatrician in Darjeeling, gave a presentation of an overview of ‘difficult children.’ He described a ‘difficult child’ as one of who was not very intellectually backward than an average child, capable of being educated but

showed abnormalities or deviation in the area of sensitiveness, inclination and volition.³

The first description of the autistic disorder is defined entirely based on the impairment in social interaction, communication, and stereotyped repetitive behaviour.⁴ In 1980, the American Psychiatric Association (APA) proposed the official title for this disorder as “Pervasive Developmental Disorder” (PDD).⁵ Besides APA, World Health Organization (WHO) also released a term definition of Autism Spectrum Conditions (ASC) as a group of childhood-onset neurodevelopmental disorders characterised by impairments in social interaction and communication, with the presence of repetitive and stereotyped behaviours, interests and activities.⁶ Besides the DSM, there is also International Classification of Diseases 10th edition (ICD-10) which describes autism in three dimensions of behaviours, deficits in social reciprocity, deficits in communication, and presence of restricted interests and repetitive behaviours.⁷

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Generally, the most common and first noted symptom of ASD in children are delays in speech and language development, followed by abnormal social responsiveness, and several nonspecific difficulties related to sleeping, eating and paying attention.^{8,9} The tell-tale signs of people who have ASD as described by the American Psychiatric Association includes communication deficits, dependence on routines, high sensitivity to changes in their environment, and intensely focusing on inappropriate items.¹⁰ Besides these primary symptoms, autistic children sometimes also exhibit severe behavioural problems, such as self-mutilation and aggression, in response to the demands of their environment, in addition to abnormal sensitivity to sensory stimuli.^{11,12} Besides communication and behaviour problems, disruption in motor abilities are also common to be found in children with ASD.¹³ Despite the lack of cognitive function in children who suffers from ASD, there are also many high functioning children whose diagnosed with autism spectrum disorders who possess average or high IQ and be able to attend regular classrooms.¹⁴

Despite the multiple theories that developed to explain the basic mechanism which causes ASD, several studies have proposed immunological, neurological, genetic, and environmental factors as possible contributors to this complex disorder.¹⁵ Theories such as problem in the development of the central nervous system, disrupting social interaction and limited and repeated behaviour are also presented.¹⁶ These findings support that the brain is both structurally and functionally different from normal¹⁷⁻¹⁹ and some found abnormalities in specific regions of the brain such as frontal and parietal parts, cerebellum, amygdala and hippocampus region in children who have ASD.^{20,21} Disruption in prefrontal cortex seems to be the one that manifests into repetitive behaviours, weakness to start or continue a new action, and a more tendencies towards the earlier works which often shows in people with ASD.²²⁻²⁴ Another study shows that children with ASD have problems in their cerebral perfusion, having inflammation, oxidative stress, and mitochondrial dysfunction, which might play a role in determining the severity the disease.²⁵ Nerve damage by inflammation, also, has been implicated in causing many conditions and complaints that are often experienced by children with autism.²⁶

For years multiple strategies and approach are already developed and implemented to provide treatment for children with ASD. Among several interventions to treat ASD, behavioural interventions are currently the most successful treatment for autism.²⁷ Besides the rehabilitation

therapies, autistic children also need additional pharmacotherapy for maintaining mood, behaviour regulation, impulse control, improve sleep and thought disorder symptoms.^{28,29} It also to help to decrease problematic behaviours, such as self-injurious behaviour, aggression and irritability.³⁰ Separate studies found that hyperbaric chamber which shows that autistic children might benefit from increased cerebral perfusion during treatment.^{31,32}

One particularly interesting topic was the occurrence of Cerebral Venous Thrombosis in ASD patients. Cerebral Venous Thrombosis (CVT) is commonly described as an occlusion of intracranial venous sinuses and cerebral veins, which can disturb the venous drainage and eventually can induce intracranial hypertension and venous infarcts.³³ Even though this case is mostly found in adult patients, based on the brain Magnetic Resonance Imaging (MRI) results performed on our paediatrics patients who have symptoms like communication and attention problems, which commonly reflect the ASD symptoms, were showing the signs of CVT. CVT usually present with chronic neurological symptoms such as headache, visual impairment, even cranial nerve VI palsies related to increased intracranial pressures, other symptoms might be related to venous infarction which ranging from developmental delays, learning disabilities, hemiparesis and hemisensory loss.³⁴ However, symptoms related to developmental delay in children who diagnosed with CVT were also noted and described in literature, for example a study by Carvalho et al.³⁵

In the management of CVT cases in the paediatric population, several therapeutic strategies are already introduced such as fluid therapy, antibiotics for the suspected infection, antiepileptic drugs for seizure control if necessary and medications to reduce intracranial hypertension.³⁶ Another treatment strategies are standard or low molecular weight heparin for 7–10 days followed by oral anticoagulants for 3–6 months. Thrombolytic and also mechanical thrombectomy are sometimes used for extensive thrombosis of superficial and deep venous structures.³⁷ A series of studies show that improved cognitive outcome might be achieved in the anticoagulated group.³⁸

The delivery method of anticoagulants therapy may vary based on each policy in the various medical facility. In RSPAD Gatot Soebroto Jakarta, the Digital Subtraction Angiography (DSA) method was modified by Terawan, which not only used as diagnostic tool but also for therapeutic goal for certain cerebrovascular disorder. One of the benefits of utilising DSA as a diagnostic modality

is the advantages of looking at all three blood flow phases, i.e. arterial, capillary and venous, especially important for cerebrovascular disease.^{39,40} According to Terawan et al. modified DSA (Digital Subtraction Angiography) procedure can appropriately be used as a delivery method of anticoagulation therapy directly to the occluded vessels. This method was later called as IAHF (Intra Arterial Heparin Flushing), which the principal difference between IAHF and the original DSA was the continuous directed local flushing of heparin into the occluded vessels.⁴¹ This study aims to present an initial result the effect of IAHF to the autism symptoms when used as a treatment for CVT in ASD patients.

METHODS

This study was a prospective case series of IAHF procedure to treat CVT in ASD patients conducted at the Cerebrovascular Centre RSPAD Gatot Soebroto Jakarta-Indonesia through 2018 until 2019. The subjects were thoroughly examined by our Autism Multidisciplinary Team. After the clinical diagnosis was established a series of examination such as routine blood work, performance test, motor evoked potentials and brain MRI was performed on these subjects. All of this examination aims to compose the most reliable information about the characteristics of the disease and from then to create the most effective therapeutic strategies. The main focus of this study was to described and compare the CARS results score before and one month after the IAHF procedure designed to treat the CVT. The Indonesian version of CARS was attached in

supplementary files. The results were then displayed in this study as a table without revealing the patient personal information and then described in the narrative.

A modified DSA procedure or IAHF used as a delivery method of anticoagulation therapy directly to the occluded vessels. This method was introduced by Terawan et al. DSA itself consist of a procedure where the femoral vein was punctured, and then the catheter was inserted through the puncture wound using a guidewire. Continuous flushing of the sheath with heparinised saline was maintained throughout the procedure, the dosage of heparin was 5000 IU of heparin in 500 cc Sodium Chloride solution. Sonographic guidance was required in some smaller children with no or barely palpable pulses. After procedure, the patients were monitored for unwanted side effects, including local, systemic, and neurologic complication. All IAHF procedures were performed by the experienced interventional radiologist at RSPAD Gatot Soebroto Jakarta.

RESULTS

We present the patient brief characteristic distribution, and the CARS result in [Table 1](#). In this study, we present a total of 10 children with ASD treated with IAHF, in which the CARS Score are measured before and after the intervention. [Table 1](#) shows the summarised characteristic and CARS results of the subjects.

[Table 1](#). above shows that male was dominant in this study and only three subjects are categorised into adolescent (≥ 10 years old). We categorised the symptoms into three main symptoms that mostly present in children with ASD, communication, attention and behaviour. From these three, the communication problem is the most common symptoms found. From a total of 10 subjects, only two among ten subjects which do not show any difference in total CARS Score. Meanwhile, one subject shows the most significant changes in CARS score as much as 9 points of a decreased total score which makes the subject status improved from moderate autism to mild autism. In this study, there is no other unwanted side effect that occurs.

DISCUSSION

The previous study showed that ASD was more common in male. The presentation of male dominance which has ASD in this study, coincidentally was quite similar with the study conducted by Whiteley, et al. in the UK.²⁶ Findings by Whiteley, et al. shows that the ratio of autistic patients between males and females was 7:1. The dominance of male patients also revealed by

Table 1. Subject Characteristic and CARS Score Before and After IAHF Intervention

NO	AGE (years)	SEX	SYMPTOMS			CARS SCORE	
			Communication	Attention	Behaviour	Before IAHF	One month after IAHF
1.	11	Male	•			48	48
2.	9	Male	•			44	40
3.	10	Male	•		•	40	31
4.	3	Female	•			45	44
5.	5	Male	•		•	34	32
6.	8	Male	•	•		40	38
7.	10	Male	•	•		35	32
8.	8	Male	•		•	32	32
9.	7	Female	•	•	•	58	55
10.	7	Male	•	•		37	32

THE CHILDHOOD AUTISM RATING SCALE (CARS)									
NO	ASPEK	NILAI				DESKRIPSI			
		1 (normal)	2 (ringan)	3 (sedang)	4 (berat)	Pre DSA	1 mngg post DSA	1 bln post DSA	2 bln post DSA
1	Hubungan dengan orang lain	Tidak ada kesulitan, sesuai umur	Tidak mau melihat mata, menoleh berlawanan, mendekati orang berlawanan	Asuh terhadap beberapa orang lain, minat minimal/terpaku, anak hanya memuli sedikit keterlibatan reaksi	Sangat jauh	3	2	2	2
2	Intai	Dapat meniru kata-kata, suara & gerakan sesuai umur	Meniru tingkah laku sederhana, perlu usaha keras, ada keterlibatan reaksi	Kadang-kadang meniru/terlalu stimulasi terus-menerus, ada keterlibatan reaksi	Tidak pernah meniru suara, gerak, kata	3	3	2	2
3	Respon Emosi	Sesuai umur, ditandai perubahan ekspresi, postur, atau tingkah laku	Tidak sesuai & tidak berhubungan dengan objek di lingkungan	Emisi & derajat respon abnormal oleh. Reaksi kurang baik, tidak berhubungan dengan situasi sebenarnya. Impulsif, terpacu	Respon tidak sesuai situasi. Tidak berubah bila mendapat mood tertentu. Reaksi emosi hebat, impulsif	2	2	2	2
4	Penggunaan Tubuh	Kemampuan gerak, koordinasi sesuai umur	Gerakan agak abnormal, umis, clummines, gerakan repetitif, kood, kurang baik, sedikit gerak aneh	Tingkah laku & gerak aneh jelek, mis. posisi tubuh aneh, meletakkan ke satu bagian tubuh, gigitan-gigitan, berputar-putar, memuntahkan	Gerak aneh mematap & hebat. Gerak tak mudah ada waktu dicoba dihentikan/diberi alternatif lain.	2	2	2	2
5	Penggunaan Objek	Perhatian & penggunaan benda/benda/ mainan normal.	Kehilangan minat thd mainan. Penggunaan mainan tidak sesuai umur, mis. Dibuang/dibuang	Kehilangan minat/hanya suka mainan tertentu dengan cara yang aneh. Mis. Tertarik pada bag. fit, pantelan cahaya dll	Frekw. & intensitas makin tinggi. Anak sulit dibalikkan perhatiannya pada yang lain	2	2	2	2
6	Adaptasi terhadap perubahan	Anak berinteraksi terhadap perubahan rutinitas, dapat beradaptasi & tak terganggu	Anak tidak terpengaruh	Menunjukkan reaksi yang agak berbeda.	Menunjukkan reaksi marah / inadaptif/terganggu	2	2	2	2
7	Respon Visual	Sesuai dengan umur, kood, visual-motorik untuk ekspresi objek	Terdapat harus dirangsang untuk melihat objek, lebih suka kaca, cahaya	Sering dirangsang untuk sesuatu bergerak, menghindari kontak mata, melihat benda dari bag./sulut tertentu	Selalu menghindari kontak mata atau objek tertentu. Menunjukkan bentuk berat dari gejala di atas	3	3	2	2

NO	ASPEK	NILAI				DESKRIPSI			
		1 (normal)	2 (ringan)	3 (sedang)	4 (berat)	pre DSA	1 mngg post DSA	1 bln post DSA	2 bln post DSA
9	Kecap, penciuman, & sentuhan	Reaksi sesuai stimulasi. Bereaksi terhadap rasa sakit biasa, tidak berlebihan	Senang memasukkan benda ke mulut, memuntahkan/memasak obj, yang sebelumnya tidak ada rasa/bau, reaksi berlebihan/ kurang terhadap nyeri	Terpaku pada menyentuh, memuntahkan/memasak objek Reaksi berlebihan/ kurang terhadap nyeri	Sifatnya bukan ekspresi, tapi persepsi. Sama sekali tidak takut terhadap rasa sakit sesuatu yang baik	3	2	2	2
10	Takut/Gelisah	Reaksi sesuai umur & stimulus	Menunjukkan takut yang berlebihan/kurang terhadap situasi gelap	Lelah Berat	Rasa takut meningkat, sulit ditanggulangi / sama sekali tidak takut terhadap apapun	2	2	2	2
11	Komunikasi Verbal	Komunikasi sesuai umur & situasi	Terdapat bicara. Bicara mudah beranti, ada echolalia/terbalik-balik. Masih mengucapkan kata/frasa	Bicara tidak ada. Bila ada merupakan kata yang diimpor & aneh, terpacu, eholalia/ kata terbalik, Pertanyaan	Tidak ada yang dapat diimpor. Suara, kata & Bahasa aneh /bahasa planet	2	2	2	2
12	Komunikasi non verbal	Sesuai umur & situasi	Kurang menggunakan bhs non verbal, biasanya dengan menunjuk/marah suatu benda	Tidak dapat menggunakan bhs. Tidak mengerti bila diperintah dengan bhs-nya.	Menggunakan kata aneh & tidak dapat diimpor. Tidak ada perhatian thp ekspresi wajah/isyah yang ditunjukkan	2	2	2	2
13	Aktivitas	Sesuai umur & situasi	Lebih aktif atau agak malas. Derajat aktivitas tidak atau menanggapi panampilan & kemampuan	Hiperaktif/ultra tidur. Sebeliknya dapat sangat diam.	Derajat hiperaktif /hipoaktif berat	3	3	3	3
14	Derajat & Konsistensi respon intelektual	Normal & konsisten	Tidak sepadan anak pada umumnya. Ada keterlibatan perkembangan.	Secara umum tak sepadan anak umumnya. Tapi di satu sisi atau beberapa fase perkembangan hampir normal dibandingkan dengan anak lain.	Secara umum tak sepadan anak umumnya. Terjadi di satu atau beberapa fase perkembangan hampir normal dibandingkan dengan anak	2	2	2	2
15	Penerimaan Menerima	Normal.	Ringan	Sedang	Berat	3	3	2	3
SKOR TOTAL						37	34	32	32

SKOR
 15-30 : NON AUTISTIC (BUKAN AUTIS)
 31-36 : MILDLY/MODERATELY AUTISTIC (AUTIS RINGAN)
 37-48 : MODERATELY AUTISTIC (AUTIS SEDANG)
 49-60 : SEVERELY AUTISTIC (AUTIS BERAT)

DIAGNOSA : Autis Sedang (batas bawah)

Figure 1. Bahasa Indonesia version of CARS

another meta-analysis that suggests that the widely reported 4:1 ratio of boys to girls is reported entirely consistent across studies, geographical regions, ethnicities, and time.⁴²

If we trace for a possible explanation, a theory that might explain this domination of male sex in ASD disorder related to the dominant male production of testosterone while females produce more estrogen. Both hormones have the opposite effect on a brain-functioning gene called Retinoic acid-related Orphan Receptor Alpha (RORA), located in the brain neurons. Testosterone can inhibit RORA action, meanwhile, estrogen improves the performance of RORA. The inhibiting mechanism of RORA performance can cause various body biological problems, such as disruption of the biological clock or a circadian rhythm that impact on sleep patterns.

Based on the symptom's category, most of the subjects had communication and attention problem, which is the most common problems that often complained by the patient's parents. This communication and attention problem often make the children with ASD seems to live inside their world, which makes them quite difficult to be instructed or educated in a general manner. However, it does not mean they are more inferior than their friends of the same age, and they have a different process to perceive their surroundings.

Although multiple diagnosing methods for ASD are developed for years, one of the most known and used methods was CARS. It is widely known as a reliable tool and already translated into multiple languages around the world. In our centre, we also use a Bahasa Indonesia version of CARS in which we used in this study. This study showed that the overall total score of CARS decreases, or in other words, there is an improvement in the children ASD status. We can see from the result table above that most of the subjects shows a decreased total score of CARS which reflects a better outcome.

Besides the conventional ASD therapeutic strategies such as behaviour therapy which proven to have a beneficial and useful results²⁷ and conventional drugs such as Risperidone which effective in maintaining problematic behaviour⁴³ and Hyperbaric Chamber³¹ in this study the subjects also undergo the IAHF therapy since they also have the CVT characteristic in their imaging results. Heparin is the chosen anticoagulant in this study since its relative safety in paediatric patients, and it is flexibility to reverse it is unwanted effects. The reasoning behind the therapeutic approach of using anticoagulant is based upon the cerebral hypoperfusion which suggested as one of the source of problem in children with ASD.²⁵

From the subjective evaluation of the child parents, there is a trend of clinical improvement. Meanwhile, for the objective manner, we suggest the parents bring their children to our facility for further follow up once every month at least for a year. However, since most of this patient are originated from outside the city even outside the country, we usually follow up these patients through conventional communication method, in this case, are direct phone call or through instant messaging. For some parents who can come to our facility for a follow up every month, we usually perform behaviour monitoring through CARS and several routine examinations, and we also order MR Perfusion to monitor the patient cerebral perfusion. From which we can compare the patient brain perfusion before and after IAHF procedure.

There no intraprocedural or iatrogenic complications noted during the procedure. Even after following up through communication media such as telephones or instant messaging to the parents after the procedure there was no complication reported. Some potentials complications could emerge from the procedure such as hematoma, oedema or bleeding at puncture site, nausea and vomiting. In this procedure there is also a risk of allergic reaction to contrast agents since it is an essential substance in angiography procedure. There is also a risk for neurological

complications such as headache, neurological deficit, or death. Despite its ability to achieve recanalisation or patency of thrombosed intracranial sinuses, the concern of safety and availability are still the main limitations of this type of thrombolysis therapy.

The authors were fully aware that this study cannot fully represent the whole case of ASD in paediatric population especially of those who also accompanied with CVT since the patient's heterogeneity is quite broad, and the total sample of this study is not quite sufficient. However, through this initial study, the authors hope to introduce a complementary therapeutic approach for ASD, especially of those who also have problems in their brain vasculature, in this case, is CVT. Further research with adequate sample size and sufficient time for monitoring is still needed.

CONCLUSION

In this study, we found that children who had ASD might also have a comorbid condition in their brain anatomy such as CVT. Whether there is an association or causality between CVT and ASD, it needs to be verified by another study. This study found that when the CVT was treated with anticoagulant therapy delivered through the DSA technique in patients with ASD, we found an improvement in the children autism clinical status. We realise that there is still further research to verify our result. Therefore, we are open for critics, advice and even further cooperation to reach a common conclusion to define this potential alternative therapy for children with ASD.

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AUTHOR CONTRIBUTION

All authors have contributed equally to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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