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Cerebral Sinovenous Thrombosis (CSVT) in a Neonate: MTHFR Mutation

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Abstract: Cerebral sinovenous thrombosis (CSVT) is an uncommon but serious condition in neonates. Because of varying manifestations, the diagnosis and management of CSVT in neonates is difficult. A 5-day male neonate was diagnosed with CSVT after the initiation of suspicious movements. The contractions were controlled and after performing diagnostic tests, the diagnosis of CSVT was made. In this report, the diagnosis and management of this rare condition in a neonate are described to highlight the importance of this serious condition in neonates.

Keywords: Cerebral Sinovenous Thrombosis, CSVT, Neonate.

1. INTRODUCTION

Cerebral sinovenous thrombosis **(**CSVT) is a very rare condition in neonates and infants and it is often underdiagnosed. The condition can cause many different and unspecific manifestations [1]. Unlike in adults with CSVT, the use of anticoagulation therapy in children, particularly in neonates, is still controversial. Timely diagnosis and management are essential given that CSVT is a potentially life-threatening condition [2]. Indeed, delays in or failure to diagnose CSVT can lead to acute or sub-acute progressive neurologic deterioration, coma, and death. However, Literature is consists of only a few case reports and case series on CSVT [3]. In this study, we aimed to report a neonatal case of CSVT attended in our hospital with suspicious movements and the steps toward the diagnosis to highlight the impact of early diagnosis and management.

2. CASE PRESENTATION

A 5-day male neonate born by C/S to a 29 years old mother of 5th gravity and 1 parity was referred to our hospital for suspected drug-resistant seizures. Gestational age was 38 weeks with a history of gestational diabetes mellitus (GDM), but no other history of maternal conditions, urinary tract infection (UTI), or hypertension. His parents were relatives (cousins). During pregnancy, the mother had used heparin because of a history of four times abortion. In this pregnancy, the mother also had received insulin due to gestational diabetes. The neonate was weighing 3700 g, with a height of 50 cm and head circumference of 35 cm. The Apgar score was 9 at minute 1 and 10 at minute 5. On physical examination, Moro, grasp and sucking reflex were normal. No sign of increased intracranial pressure (ICP) including papilledema or bulged fontanel was observed.

Parents reported suspicious movements have started on the second day of birth. He had received phenobarbital, ampicillin, and gentamicin, but suspected movements were not controlled. On the fourth day of birth because of exacerbated movements, the dose of phenobarbital increased, the patient's antibiotic was changed to amikacin and cefotaxime and referred to our hospital.

In the NICU ward of our hospital, the patient received oral topiramate, and levetiracetam, vitaminB6 through the intravenous line. During the examination and after receiving anticonvulsant medication, the patient was visited. The patient was lethargic and had a contraction on the lower and upper extremities during the examination, which did not appear to be of a seizure nature. After this neurologic exam, severe jitteriness became increasingly suspected, but medications continued.

Trans-fontanel ultrasound was performed on the day of admission which revealed irregular and prominent Choroid plexus on lateral ventricle suggestive of intra-ventricular hemorrhage (IVH grade 3 or 4). The neurologic consult was requested and electroencephalogram (EEG) and computerized tomography (CT) scan of the brain were performed to assess intracranial abnormalities which revealed bilateral IVH, thus Brain Magnetic resonance imaging (MRI) and Magnetic Resonance Venography (MRV) were requested. Brain MRI revealed blood-CSF level in dependent portions of occipital horns of lateral ventricles; suggestive of IVH. Distension, increased signal and lack of flow seen in trochlea heterophili, left transverse sinus and part of the left sigmoid sinus and superior sagittal sinus were indicative of sinovenous thrombosis. Acute left frontoparietal ischemic infarction was noted that showed restriction on DWI/ADC maps (Figure 1). On echocardiogram small atrial septal defects (3.5-4.5 mm) was reported. The laboratory tests were ordered of which the results are summarized in Table 1.

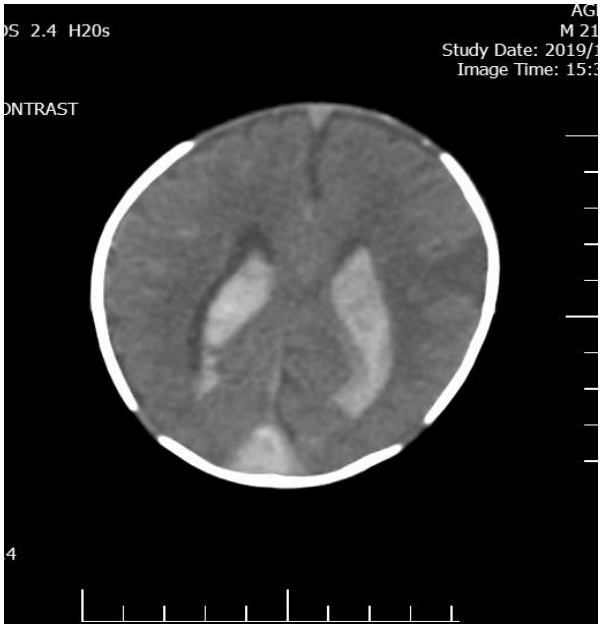
Table 1: Results of laboratory tests

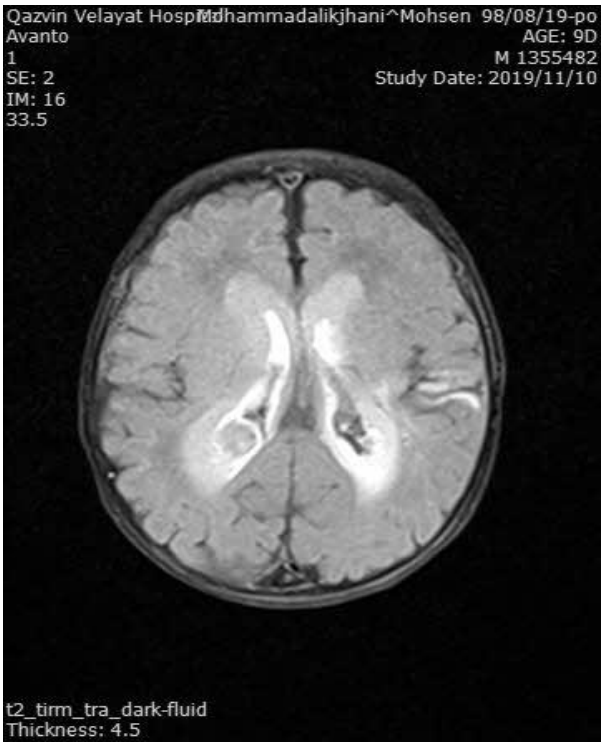
Laboratory tests	**Results**
ammonia	0.3
Lactate	20.4
PT	12.8
PTT	36
INR	1
Ca	9.2
BS	91
Mg	2.14
BUN	3.7
Creatinine	0.82
CRP	2.1
WBC	12300 (PMN: 65.2%, Lymph: 21.6%)
Hb	17.3
PLT	233000

After the mother took prenatal tests, it was found that the mother had a high level of homocysteine and was in treatment with heparin who had not consumed the medication for 15 days in late pregnancy. After hematologic consultation the following experiments were requested: factor assay; pr C &S; Antithrombin 3, factor 5 Leiden and, G20210A mutation were normal.

The patient went on a healing process from the 19 day without any further development of other Complications and then was discharged from NICU with prescribed oral levetiracetam 0.7 cc BID(q12h) and phenobarbital 15 mg ½ BID and suggesting follow up laboratory tests and Serial brain ultrasound for reassurance.

On brain ultrasound performed at 1 month ,lateral ventricle hydrocephaly with 17 and 14 mm diameter on the atrium and dilated the third ventricle was reported. In the evaluations performed, coagulation factor assays were normal, serum homocysteine was 17μ mol/L (mildly elevated) and, wild type homozygote for MTFHR 677C>T (Ala222Val) was reported. At the present moment, the patient is one-year-old and is under treatment with Levetiracetam, phenobarbital, folinic acid, vitamin B6, and occupational therapy. During the first year of life the development was normal. He can stand with help, but paresis is obvious on the right side of the body.

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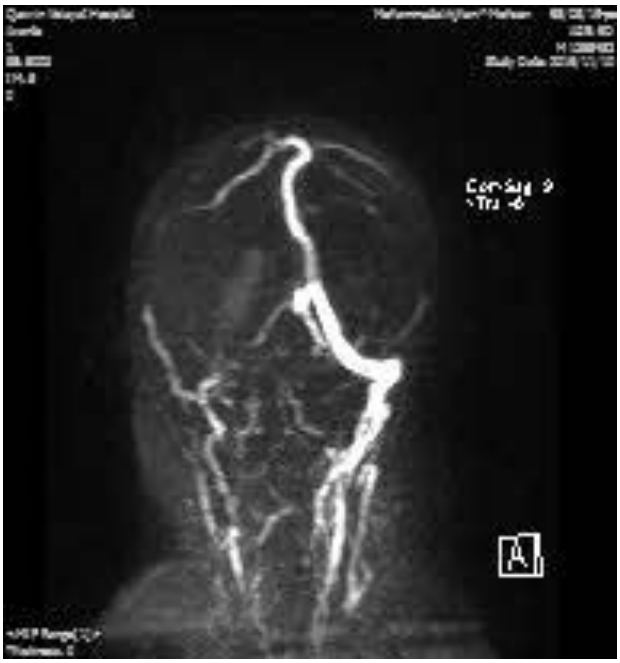

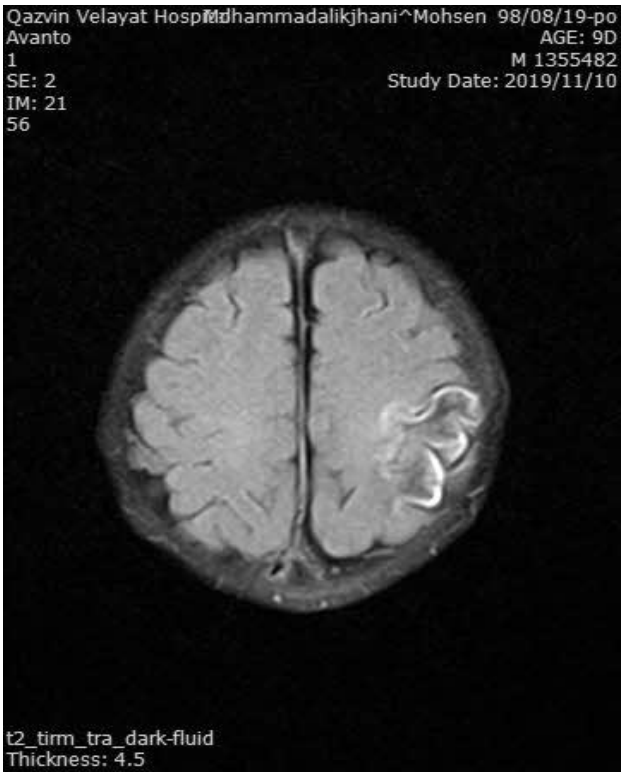

Figure 1 Brain MRI and MRV

3. DISCUSSION

CSVT is a very rare condition in pediatrics. Based on studies the incidence is 0.25 to 0.67 in 100,000 children every year [4]. But the condition may have a serious impact on cognitive and neuromotor development. Hence it is important to make an early diagnosis to prevent such effects. CSVT presents a very wide and non-specific range of signs and symptoms which makes the diagnosis difficult [5].

The clinical symptoms would like to develop gradually and insidiously and frequently occur as encephalopathy, headache, lethargy, agitation, nausea, vomiting, and visual disturbance. Epileptic seizures and diffuse neurologic symptoms and signs (encephalopathy, headache) are more common than focal deficits (hemiparesis, hemisensory loss, aphasia, and ataxia) [6]. Signs of raised ICP including papilledema, abducens nerve palsy, and visual field deficits resulting from optic nerve compression may also be found on neurologic examination. Signs and symptoms of increased ICP secondary to CSVT are clinically indistinguishable from those seen in pseudotumor cerebri syndrome (PTCS). Therefore, a diagnosis of PTCS should not be made without first excluding CSVT by neuroimaging [7].

Many different risk factors and comorbidities are associated with CSVT in pediatrics. CSVT happens more frequently in neonates and males and is mostly associated with prothrombotic disorders, dehydration, systemic infection, head and neck infection, other head and neck disorders, hematological disorders, malignancy, and cardiac diseases [8]. Prothrombotic disorders have been reported in 20% to 80% of pediatric patients with CSVT, although their role in pathogenesis is not fully understood. Specific prothrombotic disorders reported in pediatric CSVT studies include genetic thrombophilias such as mutations in Factor V Leiden and Prothrombin G20210A genes. The latter appears to significantly increase the risk of recurrent thromboembolism in children older than 2 years, especially in

the setting of an additionally acquired coagulopathy. Other identified prothrombotic disorders include the presence of anticardiolipin antibodies, elevated lipoprotein (a), and deficiencies of protein C, protein S, and antithrombin [9, 10]. Both hyperhomocysteinemia and MTHFR homozygosity appear to be associated with childhood and adult CSVT [11, 12]. MTHFR is the main element playing role in the folate cycle and contributes to the metabolism of homocysteine via facilitating the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, and therefore, producing the active form of folate required for re-methylation of homocysteine to methionine [13]. In this respect, deficiency of MTHFR might give rise to elevated plasma homocysteine, which in turn is accompanied by an increased risk of vascular diseases. This issue has been supported by previous literature where the mutation of MTHFR is shown to be associated with increased risk of CVST.

Our case was presented with jitteriness a rarely reported manifestation. Fortunately, the patient was not missed and the essential steps toward the diagnosis were taken to reach an acceptable outcome. It seems that in our case the hyperhomocysteinemia and discontinuation of heparin by the pregnant mother predisposed the patient to a hyper-coagulopathy state. These factors along with male gender (a source of high production of testosterone) are believed to be the underlying etiology of CSVT.

In conclusion due to wide and unspecific manifestations of the CSVT, physicians and pediatricians should have CSVT diagnosis in mind to prevent irreversible impacts of this condition in the future life of neonates.

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