Case Report
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A Rare Case of Cerebral Sinovenous Thrombosis Associated with *MTHFR* A1298C and C677T Mutations

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ABSTRACT

Neonatal cerebral sinovenous thrombosis (CSVT) is a rare disease with severe neurological sequelae. *Methylenetetrahydrofolate reductase* (*MTHFR*) is a key enzyme in the folate cycle, and mutations in *MTHFR* are associated with vascular diseases. Here, we report the case of a newborn with *MTHFR* mutation-associated CSVT. Analysis of *MTHFR* in the patient detected heterozygous C677T (677CT) and A1298C (1298AC) mutations. Analysis of *MTHFR* in the patient's mother did not detect a C677T (677CC) mutation but detected a homozygous A1298C (1298CC) mutation. Our results suggest that the presence of heterozygous *MTHFR* C677T and A1298C mutations affect thrombophilic activity in the neonate, resulting in the development of refractory seizure and CSVT. Moreover, presence of the homozygous *MTHFR* A1298C mutation in the patient's mother, who did not show any symptoms associated with thrombophilic activity, and conditions during gestation may have affected the patient's condition.

Key Words: Methylenetetrahydrofolate reductase, Cerebral infarction, Newborn, Stroke, Thrombosis

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INTRODUCTION

Cerebral sinovenous thrombosis (CSVT) is a rare form of ischemic stroke that affects neonates and in approximately half of all cases, results in neurological impairment or death. *Methylenetetrahydrofolate reductase* (*MTHFR*) synthesizes 5-methyltetrahydrofolate, a circulatory form of folate, that converts homocysteine to methionine[1,2]. *MTHFR* plays a central role in the folate cycle, and mutations in *MTHFR* are associated with vascular diseases[1,2]. This outcome is thought to be associated with hyperhomocysteinemia that switches the normal antithrombotic phenotype of the endothelium, thus inducing venous thromboemboli and other thrombotic events[3,4].

C677T is the most common missense mutation and the best characterized polymorphism in *MTHFR*, followed by A1298C[2,5]. Few case reports have described an association between neonatal CSVT and *MTHFR* mutations[6,7]. Moreover, none of these case reports have described an association between CSVT and the *MTHFR* A1298C and C677T mutations.

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Herein, we report the case of a newborn with CSVT who developed refractory seizures and harbored *MTHFR* A1298C and C677T mutations.

CASE REPORT

A newborn baby was transferred to our neonatal intensive care unit from a local obstetrics unit after experiencing a seizure. The seizure began 90 min after birth and was a generalized tonic-clonic-type seizure. The neonate was born after 39 weeks of gestation, had a birth weight of 2,658 g, and was delivered by emergency cesarean section because of fetal distress. Perinatal examination yielded normal results. The patient had a healthy elder brother aged 4 years.

The patient had status epilepticus at the time of admission, which lasted for 90 min, and had lost consciousness. Light and deep tendon reflexes of the patient were normal. However the patient showed rigidity throughout the body. The patient was administered phenobarbital at a loading dose (20 $mg \cdot kg^{-1} \cdot day^{-1}$; Jeil Pharmaceutical, Korea) and empirical antibiotics (cefotaxime and ampicillin-sulbactam) at our facility. However, administration of phenobarbital did not control the seizure. Therefore, the patient was administered phenytoin (4 $mg \cdot kg^{-1} \cdot day^{-1}$; Hanlim Pharmaceutical, Korea) and midazolam (0.01 $mg \cdot kg^{-1} \cdot h^{-1}$; Bukwang Pharmaceutical, Korea). Thus, the seizure was controlled by administering phenobarbital, phenytoin, and midazolam.

Contrast-enhanced brain computed tomography (CT) performed on day two following birth showed diffuse dural sinus thrombosis in the superior sagittal, straight, and bilateral transverse sinuses (Figure 1). Therefore, continuous heparin therapy (28 units $\cdot kg^{-1} \cdot h^{-1}$; Greencross, Korea) was initiated for the patient from day two of hospitalization. Contrast-enhanced brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) performed on day 13 of hospi-

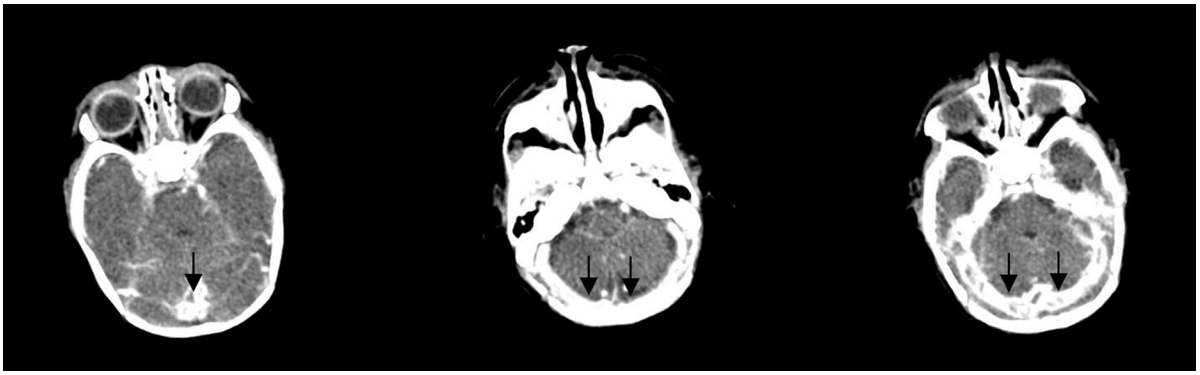

Figure 1. Contrast-enhanced brain computerized tomography (CT) on day 2 of hospitalization. showing diffuse dural sinus thrombosis in the superior sagittal, straight, and bilateral transverse sinuses (black arrow).

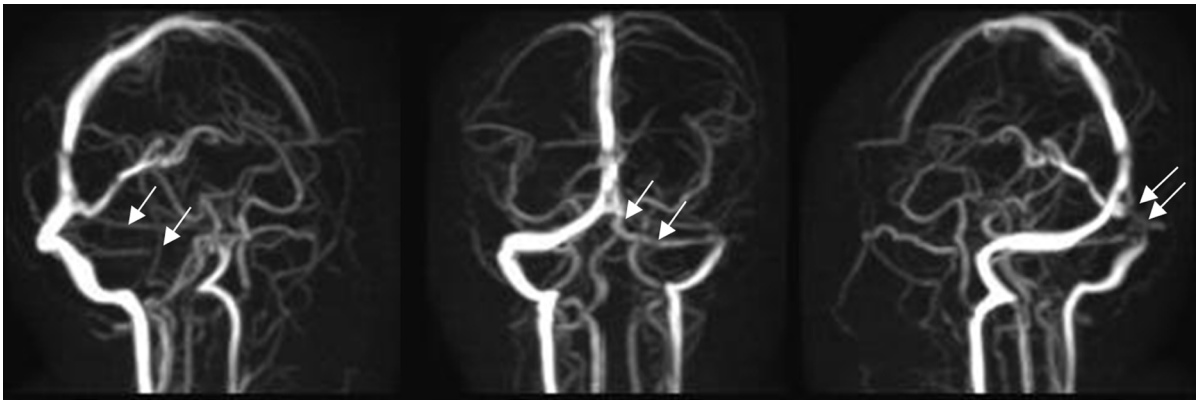

Figure 2. Contrast-enhanced brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) on day 13 of hospitalization showing suspicious residual thrombosis in the bilateral transverse sinuses and a small, hypoplastic left transverse sinus (white arrow).

talization detected suspicious residual thrombosis in the bilateral transverse sinuses. A small, hypoplastic left transverse sinus was also detected, but not any abnormal signal intensity in the brain (Figure 2). Moreover, laboratory analysis performed on day 15 of hospitalization to determine thrombophilic activity showed that the levels of protein-C, protein-S, factor VIII, antithrombin III, factor V Leiden, and anti-phospholipid antibody were within normal limits. Moreover, the patient tested negative for the prothrombin G20210A mutation.

Analysis of *MTHFR* in the patient detected a heterozygous C677T (677CT) and A1298C (1298AC) mutations. Analysis of *MTHFR* in the patient's mother did not detect a C677T (677CC) mutation, but detected a homozygous A1298C (1298CC) mutation. Analysis of *MTHFR* in the patient's father detected a heterozygous C677T (677CT) mutation but did not detect an A1298C (1298AA) mutation (Figure 3).

The patient experienced subtle seizures and showed rigidity throughout the body despite the replacement of the anticonvulsant agent with a continuous infusion of valproate sodium (5 mg·kg^{-1} · h^{-1}; Samjin Pharmaceutical, Korea) and levetiracetam (20 mg·kg-1·day-1; UCB Korea Pharmaceutical, Belgium) on day 13 of hospitalization. From day 20 of hospitalization, the patient was administered warfarin (0.2 mg·kg^{-1} · day^{-1}; Hana Pharmaceutical, Korea) in place of continuous heparin therapy. Warfarin therapy was continued until day 80 of hospitalization. The patient did not show any complications associated with heparin and warfarin therapies. An electroencephalogram (EEG) obtained on day 33 of hospitalization showed intermittent generalized bursts of high-amplitude irregular spike and wave discharge and background suppression, indicating diffuse cerebral dysfunction. Contrast enhanced brain MRI performed on day 45 of hospitalization showed resolved dural sinus thrombosis and no abnormal focal lesions in the brain parenchyma. An EEG obtained on day 50 of hospitalization showed moderate suppression of the background activity, indicating diffuse cerebral dysfunction. The patient died on day 80 of hospitalization because of aspiration pneumonia and disseminated intravascular coagulation.

DISCUSSION

Neonatal seizures are frequent and are mainly caused by hypoxic-ischemic encephalopathy and metabolic or electrolyte disorders such as hypoglycemia, hypocalcemia, and intracranial hemorrhage (ICH)[8]. Because ICH is the major cause of neonatal

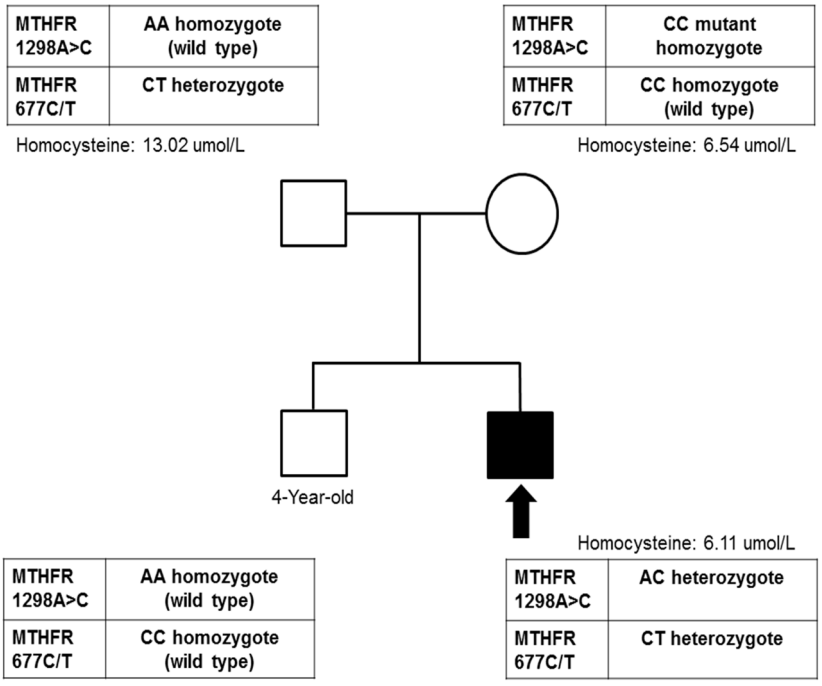

Figure 3. Pedigree of the patient's family including the status of *methylenetetrahydrofolate reductase* (*MTHFR*) A1298C and C677T mutations and homocysteine levels.

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seizures that begin soon after birth, the presence of ICH should be ruled out by performing CT or brain sonography.

CSVT is a rare disorder in neonates that results in neurological impairment, including cognitive impairment, motor impairment, or death in most cases. Potential risk factors of CSVT include acute systemic illnesses, prothrombotic state, and head and neck infections such as otitis media, mastoiditis, and sinusitis. However, many cases of CSVT remain idiopathic[9,10]. The estimated incidence of neonatal CSVT is 40.7 per 100,000 live births per year. Although both premature and term infants are at a risk of CSVT, the exact rate of CSVT in term neonates is unknown and is likely to be underestimated[9].

Known risk factors for CSVT include the presence of anticardiolipin antibody, lupus anticoagulant, factor V Leiden, and G20210A prothrombin-gene mutation, as well as decreased levels of protein C, protein S, antithrombin, fibrinogen, and plasminogen[9]. Additional risk factors for neonatal CSVT include preeclampsia and gestational diabetes[9,11]. Moreover, premature rupture of membranes, hypoxia at birth, placental abruption, meconium aspiration, fetal distress, dehydration, head and neck disorders, meningitis, and sepsis are risk factors of fetal CSVT[9,11]. The majority (81%) of infants with CSVT develop symptoms within the first week of life. However, signs and symptoms of CSVT are often subtle and nonspecific. Symptoms of CSVT include seizures, lethargy, irritability, poor feeding, apnea, jitteriness, or changes in muscle tone[11].

Radiology plays an integral role in the diagnosis of CSVT. CT and MRI are the most common noninvasive imaging modalities for assessing CSVT[12]. Studies addressing the treatment and monitoring of neonates with CSVT are lacking. Hence, large variability exists among treatments for CSVT because of the lack of optimization[13]. Evidence-based clinical practice guidelines established by the American College of Chest Physicians indicate the use of antithrombotic therapy for treating CSVT[14]. Although not supported by clinical trials, use of unfractionated or low-molecular-weight heparin is recommended for treating patients with CSVT for a minimum of 6 weeks to not more than 3 months[13,15]. A cohort study showed normal outcomes in 45% survivors, neurological deficits in 47% survivors, and persistent epilepsy in 16% survivors[16].

MTHFR is the key enzyme in the folate cycle. Moreover, it plays a role in the metabolism of homocysteine by catalyzing the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and generates the active form of folate required for the remethylation of homocysteine to methionine[2]. Rook et al.[17] reported that the homozygous *MTHFR* A1298C mutation is associated with stroke in pediatric population, with a 4-fold increase in the frequency of stroke in infants with this mutation compared with that in infants without this mutation. However the exact mechanism through which this polymorphism promotes the formation of thrombus without altering the plasma levels of homocysteine is unclear.

Few studies have reported the association between *MTHFR* mutations and cerebral stroke[6,7]. Cizmeci et al.[6] reported the case of a neonate with CSVT who had homozygous *MTHFR* A1298C mutation. Arpino et al.[7] reviewed two patients with presumed cerebral stroke who were born from two monochorionic twin pregnancies in which the other co-twin died in utero because of a maternal homozygous *MTHFR* C677T mutation and fetal homozygous *MTHFR* A1298C mutation.

Here, the patient had compound heterozygous *MTHFR* C677T and A1298C mutations, which exerted a similar thrombophilic effect as homozygous *MTHFR* C677T mutations. A study by van der Put et al.[5] indicated that patients with heterozygous *MTHFR* C677T and A1298C mutations showed significantly decreased *MTHFR* activity. The presence of heterozygous *MTHFR* C677T and A1298C mutations decrease *MTHFR* activity compared with the presence of either one alone. This in turn significantly increases homocysteine levels and decreases plasma folate levels[5].

Weisberg et al.[1] indicated that the presence of both *MTHFR* C677T and A1298C mutations further decreased *MTHFR* activity by approximately 50-62%. The studies by van der Put et al.[5] and Weisberg et al.[1] indicated that the presence of both heterozygous *MTHFR* C677T and A1298C mutations decreased *MTHFR* activity and induced a thrombophilic effect, e.g., CSVT in our case. Our patient experienced severe CSVT symptoms, as well as presenting with additional laboratory results associated with thrombophilic activity. These results included levels of protein-C, protein-S, factor VIII, antithrombin III, factor V Leiden, and anti-phospholipid antibody, as well as negative prothrombin G20210A mutation and led us to assume that compound heterozygous *MTHFR* mutations caused CSVT in our patient.

Brown et al.[18] showed that the frequencies of *MTHFR* 677CT/1298AA, 677CT/1298AC, and 677CC/1298CC genotypes were 0.228, 0.198, and 0.088, respectively. *MTHFR* mutations could be of clinical importance if they are caused by low folate intake during times requiring high amounts of folate, such as during

pregnancy[5]. The patient's mother had a homozygous *MTHFR* A1298C mutation but did not show symptoms associated with thrombophilic activity. Moreover, she was healthy and did not have any illness or family history of thrombophilic activity. Therefore, we believe that the homozygous *MTHFR* A1298C mutation in the mother and conditions during gestation affected the patient's condition.

In conclusion, *MTHFR* mutation-associated CSVT is a rare disease with serious neurological sequelae. We believe that additional large case studies are needed to understand the thrombophilic effect of the compound heterozygous *MTHFR* C677T and A1298C mutations.

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