Malignant Hyperthermia and Cerebral Venous Sinus Thrombosis After Ventriculoperitoneal Shunt in Infant with Schizencephaly and COL4A1 Mutation

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**CASE REPORT**

A 9-month-old boy weighing 7.9 kg was scheduled for a VPS for progressively increasing head circumference and hydrocephalus. He was previously diagnosed prenatally as having hydrocephalus and schizencephaly. Ultrasonography at 21 weeks of gestation showed bilateral ventriculomegaly with hypertrophic ventricular walls. A fetal brain magnetic resonance imaging (MRI) at 24 weeks showed ventriculomegaly and left cerebral hemisphere cleft (Figure 1A). He was delivered via cesarean section at 37 weeks. After birth, MRI of the head demonstrated an open-lip type schizencephaly and hemosiderin deposits in the ventricles (Figure 1B and C). He also had bilateral congenital cataracts and hemolytic anemia. At the age of 9 months, he presented with a loss of appetite and neurologic examination revealed the sunset phenomenon. His head circumference was 32.5 cm (±0.38 standard of deviation) at birth but increased to 47.3 cm (±2.0 standard of deviation) at 9 months.

**INTRODUCTION**

Schizencephaly is a rare congenital central nervous system malformation characterized by linear, thickened clefts of the cerebral mantle, extending from the pial surface to the ventricles lined by heterotopic gray matter. In a review of 734 patients with schizencephaly, 60.9% of patients had ventricular enlargement. A third of children with schizencephaly require a ventriculoperitoneal shunt (VPS) for progressive, obstructive hydrocephalus. Yoneda et al. reported that collagen type IV alpha 1 (COL4A1) mutations can cause schizencephaly and porencephaly. Type IV collagens are basement membrane proteins expressed in all tissues including blood vessels. The phenotypes of COL4A1 mutations are varied and can cause an array of systemic disorders, such as ocular, muscular, renal, cardiac, pulmonary, and intracranial disorders including white matter change, periventricular leukomalacia, stroke, aneurysm formation, and epilepsy. We need to better understand the wide spectrum of phenotypes for better perioperative management. To the best of our knowledge, malignant hyperthermia and cerebral venous sinus thrombosis (CVT) have never been previously reported in patients with COL4A1 mutations. We report an infant case of schizencephaly associated with COL4A1 mutation who suffered from malignant hyperthermia and CVT after VPS for hydrocephalus.

**BACKGROUND:** Schizencephaly is a rare congenital central nervous system malformation characterized by linear, thickened clefts of the cerebral mantle. Recently, germline mutations in collagen type IV alpha 1 (COL4A1) have been reported to be a genetic cause of schizencephaly as a result of prenatal stroke. Patients with COL4A1 mutation demonstrate a variety of disease phenotypes. However, little is known about the potential complications of patients with COL4A1 mutations before and after neurologic surgery.

**CASE DESCRIPTION:** A 9-month-old boy with schizencephaly and a congenital cataract underwent a ventriculoperitoneal shunt for progressive hydrocephalus. Postoperatively, he developed malignant hyperthermia and cerebral venous thrombosis. Early treatment with dantrolene sodium and hydration was effective. Genetic testing revealed a germline COL4A1 mutation.

**CONCLUSIONS:** To our knowledge, malignant hyperthermia and cerebral venous thrombosis have not been reported in the literature in patients with COL4A1 mutations after surgery. Schizencephaly arising from COL4A1 mutations might be a disease prone to these adverse effects because this mutation is known to be associated with venous tortuosity, venous vulnerability, and muscle spasms due to basement membrane protein abnormalities. We need to better understand the wide spectrum of clinical phenotypes of COL4A1 mutations and potential complications in order to better manage surgery of patients with schizencephaly.
deviation) at 7 months and 49.0 cm at 9 months. Lateral ventricle width was 30.5 cm at birth and had also increased to 52.8 cm at 9 months. His development milestones were severely delayed. He was unable to sit or control his neck. He was able to swallow and had movement of his limbs, but any type of communication was difficult at 9 months. He was transferred to the Department of Neurosurgery, Niigata University and underwent a VPS. As the left cerebral mantle had a large defect between the open frontoparietal lips (Figure 2A), VPS was performed on the right side. A programmable valve shunt system was used with a limiting pressure of 120 mm H2O. General anesthesia was maintained with sevoflurane, remifentanil, and rocuronium. Immediately after surgery, the patient’s condition was good and computed tomography obtained just after surgery showed the appropriately inserted shunt tube into the right lateral ventricle.

Six hours after surgery, his temperature suddenly rose to 38.6°C with a heart rate of 191 beats per minute and SpO2 of 93%, with muscle rigidity of the limbs and trunk. Serum creatine phosphokinase levels were 10,571 U/L and 12,257 U/L, respectively, on the day of operation and at postoperative date (POD).1 We diagnosed his condition as malignant hyperthermia, and dantrolene was started with sufficient hydration. Muscle rigidity improved, and the elevated creatine phosphokinase values returned to normal 10 days after starting the therapy. Treatment with dantrolene was completed after 4 days, and renal dysfunction was not observed. At POD 5, he recovered until he could take milk and preoperative symptoms of intracranial hypertension disappeared.

At POD 6, brain CT showed brain edema in the bilateral frontal lobes with high-density areas in the superior sagittal sinus and bilateral bridging (cortical) veins (Figure 2B, E, and G). MRI demonstrated widespread thrombosis of the entire superior sagittal sinus, vein of Galen and straight sinus, confluence, bilateral transverse sinuses, and cortical veins. Venous flow was maintained through the bilateral cavernous sinuses, inferior petrosal sinuses, and basilar plexus. Susceptibility-weighted imaging revealed many corkscrew-like medullary veins in the bilateral frontal lobes (Figure 3A–C). Anticoagulant therapy was not initiated because the patient’s vital signs were stable and he did not demonstrate any additional symptoms of CVT, and thus we did not change valve settings. Blood examination revealed normal values of platelet count, antithrombin III, proteins C and S, plasmatic homocysteine, fibrinogen, antinuclear antibodies, lupus anticoagulant, and cardiolipin antibodies. Two months later, the CVT and white matter lesions disappeared spontaneously. Blood samples were collected for deoxyribonucleic acid (DNA) analysis after obtaining approval from the Institutional Review Board of Niigata University (H28-781-2) and written informed consent from the parents. Genomic DNA was extracted from the patient, mother, and father. Whole-exome sequencing of the sample was performed as previously described.1 A de novo mutation, c.2273G > A (p.Gly758Glu) in the COL4A1 gene was detected from only the patient’s DNA.

DISCUSSION
Malignant hyperthermia and CVT developed in an infantile after VPS in a patient with schizencephaly arising from a COL4A1 mutation. These adverse events have not been reported as postsurgical complications in these patients.

A variety of clinical phenotypes including small vessels disease affecting the brain, eyes, and kidneys are associated with mutations in COL4A1. Type IV collagen comprises basement membrane proteins that are expressed in all tissues including the vasculature. COL4A1 and
COL4A2 are the most abundant type IV collagens.4 In mice models with COL4A1 mutations, electron microscopic examination shows uneven basement membranes with inconsistent density and focal disruptions of the basement membrane in cerebral vessels. Although the basement membranes in other tissues also were affected, the major site of hemorrhage was the brain.9 Porencephaly was observed in these mice after cerebral hemorrhage.

COL4A1 mutations were identified in about half of patients with schizencephaly.4 Recently, COL4A2 mutations were also reported to be a genetic cause of schizencephaly.10 Intracranial hemorrhages are frequently seen in patients with COL4A1 mutations, and the hemorrhages are attributed to fragility of the vessels.11,12 It is speculated that intracranial hemorrhages before the completion of neuronal formation and migration result in schizencephaly.5 Phenotypes of COL4A1 mutations vary in systemic and intracranial disorders4-7,9-16 (Table 1). In the present case, schizencephaly, cataracts, muscle cramps, and hemolytic anemia were recognized as associated disorders in COL4A1 mutations. In addition, hemosiderin deposition was observed on T2*-weighted images as sequelae of intraventricular hemorrhage, and CTV and malignant hyperthermia were observed after VPS.

Porencephaly, most often caused by germinal matrix hemorrhage leading to deep venous infarction with subsequent tissue necrosis and porencephalic cavitation, has also been reported to be associated with both COL4A1 and COL4A2 mutations.4 Hemosiderin deposits in the ventricles are more specific to venous infarction and suggest damage to the cerebral veins in porencephaly.13 Yoneda et al4 have recently showed that COL4A1 mutations cause both porencephaly and schizencephaly, further evidence that these 2 diseases share the same genetic background. Schizencephaly is distinguished from porencephaly, which are clefts in the central mantle that arise as the result of a destruction of the...
Schizencephaly is understood as a neuronal migration disorder because the cleft is lined by abnormal gray matter, called polymicrogyria. Conversely, porencephaly is understood to be caused by a postmigration hemorrhage resulting in cerebral damage, without gray matter lining the clefts or an associated malformation of cortical development. It has been suggested that both schizencephaly and porencephaly are caused by encephaloclastic regions, and the difference in phenotype can be attributed to time of insult. Sato et al. reported a case of schizencephaly that showed enlargement of lateral ventricles at 28 weeks of gestation, which was normal at 26 weeks. The present case also suggests that the onset or timing of damage in schizencephaly occurs during midterm.

Niwa et al. showed hemorrhages in the peripheral portion of the region of schizencephaly and intraparenchymal hemorrhages, as well as tortuosity of the veins on susceptibility-weighted imaging of a 15-month-old boy who presented with spasms. In the present case, hemosiderin deposits in the ventricles on T2*-weighted imaging and characteristically tortuous veins on SWI were observed.

Taken together, schizencephaly with COL4A1 mutations can cause venous infarction during the fetal period, and patients with germline COL4A1 mutations are prone to venous thrombosis from slow venous flow and congestion. However, there are no reports of CVT in patients with schizencephaly and only 1 previous report of CVT in pediatrics after VPS in the literature.

As muscle cramp and myopathy are common features of COL4A1 mutations, malignant hyperthermia might be induced by anesthetics and surgical stress resulting in dehydration. In the present case, early administration of dantrolene and sufficient hydration were started soon after the signs and symptoms of malignant hyperthermia appeared. Asymptomatic but massive CVT developed in the superior sagittal sinus, straight sinus, bilateral transverse sinuses, the great vein of Galen, and cortical veins, and associated venous congestion was noted. Postoperative CVT in pediatric patients has been reported after various neurosurgical interventions, such as cranial vault reconstruction, subdural empyema evacuation, and tumor resection with sinus exposure during surgery. Although the sinuses were not exposed by VPS, we speculated that a rapid change in intracranial pressure by VPS may have caused CVT and his unique genetic background cause marked venous tortuosity of veins with stagnant flow.

Regarding the treatment of CVT, anticoagulation therapy is generally considered safe. However, anticoagulation was not initiated in the present case because the patient was asymptomatic and multiple hemosiderin deposits were observed on T2*-weighted images as sequelae of cerebral hemorrhage. Only sufficient hydration was maintained, and the CVT spontaneously resolved without recurrence for over a year.

Some patients with a suspected pathologic mutation of COL4A1 or COL4A2 are clinically asymptomatic, and COL4A1 or COL4A2 mutations contribute to ~6% of sporadic late-onset cerebral hemorrhage. In our opinion, COL4A1 mutation has just recently been identified and may be underdiagnosed. Although the presence of COL4A1 mutations is not contraindicatory for surgery, these mutations may predispose to various complications. Further study of complications in patients harboring COL4A1 mutations is necessary.

In conclusion, we report a case of schizencephaly with COL4A1 mutation in which the patient suffered from malignant hyperthermia and CVT after VPS. Although both malignant hyperthermia

Figure 3. Magnetic resonance imaging was also performed 6 days after ventriculoperitoneal shunting. (A and B) Susceptibility-weighted imaging (SWI) showing corkscrew-like hypointensity signals of the bilateral frontal lobes and hypointensity of the bilateral deep venous systems. (C) SWI demonstrates thickened, cordlike areas of hypointensity over the vertex, compatible with thrombosed cortical veins.
and CVT can be fatal, early treatment intervention was effective. Recognition of a wide variety of phenotypes of COL4A1 mutations and potential complications after surgery is necessary for better management of patients with these mutations.

REFERENCES


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