Intracranial Hemorrhage and Tortuosity of Veins Detected on Susceptibility-weighted Imaging of a Child with a Type IV Collagen α1 Mutation and Schizencephaly

Tetsu NIWA1,2*, Noriko AIDA2, Hitoshi OSAKA3, Takahito WADA4, Hirotomo SAITSU5, and Yutaka IMAI1

1Department of Radiology, Tokai University School of Medicine
143 Shimokasuya, Isehara, Kanagawa 259–1193, Japan
2Department of Radiology, Kanagawa Children’s Medical Center
3Department of Pediatrics, Jichi Medical School
4Department of Medical Ethics and Medical Genetics, Kyoto University Graduate School of Medicine
5Department of Human Genetics, Yokohama City University Graduate School of Medicine
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Type IV collagen α1 (COL4A1) forms a sheet-like network beneath the endothelium and surrounding smooth muscle cells. Associations of mutations in COL4A1 with porencephaly, schizencephaly, and intracranial hemorrhages are known. We report susceptibility-weighted imaging (SWI) findings showing hemorrhages in the peripheral portion of the region of schizencephaly, intraparenchymal hemorrhages, and tortuosity of the intracranial veins in a child with a COL4A1 mutation. SWI findings may be helpful for understanding the possible relationship between schizencephaly and COL4A1 mutations.

Keywords: schizencephaly, susceptibility-weighted imaging, type IV collagen α1 mutation

Introduction

Type IV collagen is a crucial component of basement membranes including vascular membranes. Type IV collagen α1 (gene name: COL4A1) forms a sheet-like network beneath the endothelium and surrounding smooth muscle cells.1 After a new mouse with a COL4A1 mutation was shown to develop fetal hemorrhages and porencephaly, human families with infantile hemiparesis and porencephaly have also been reported as having mutations in COL4A1, which is located on chromosome 13q34.2 Recently, schizencephaly as well as porencephaly has also been reported in patients with a COL4A1 mutation.3

Susceptibility-weighted imaging (SWI) has been introduced as a magnetic resonance (MR) imaging technique that is based on blood oxygen level-dependent contrast, with additional magnetic susceptibility weighting using phase data. This technique is highly sensitive for visualizing substances with susceptibility effects, such as blood, iron, calcifications, and air.4 Accordingly, SWI yields good visualization of both intracranial hemorrhages and veins. We report SWI findings showing hemorrhages in the peripheral portion of the region of schizencephaly and intraparenchymal hemorrhages as well as tortuosity of veins in a child with a COL4A1 mutation.

Case Report

A 15-month-old boy was referred to our hospital with spasms. He had been delivered by emergency Caesarean section due to non-reassuring fetal status and underwent hypothermia therapy due to asphyxia. After the hypothermia was resolved, he ate well and gained weight. Computed tomography (CT) revealed no acute lesions, but schizencephaly and several foci of intraparenchymal spotted calcifications were seen. Clinical and serum examination revealed no evidence of congenital infection.

MR imaging of the brain was performed using a

*Corresponding author. Phone: +81-463-93-1121, Fax: +81-463-93-6827, E-mail: niwat@tokai-u.jp
3-tesla MR imaging unit (Verio, Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. MR imaging sequences included axial and coronal $T_2$-weighted fast spin-echo (SE) imaging (repetition time [TR]/echo time [TE], 5000/125 ms; slice thickness, 4.5 mm), axial $T_1$-weighted SE imaging (TR/TE, 500/9.4 ms; slice thickness, 4.5 mm), axial magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) (TR/TE, 1570/2.1 ms; inversion time, 800 ms; flip angle, 9 degrees; slice thickness, 1.0 mm), axial diffusion-weighted imaging (TR/TE, 8600/90 ms; b-factor, 1000 s/mm$^2$), MR angiography, and SWI. SWI was performed with the following parameters: TR/TE, 38/30 ms; flip angle, 15 degrees; matrix, $192 \times 256$; slice thickness, 1.5 mm; field of view, 150 mm; general autocalibrating partially parallel acquisition (GRAPPA), 2. Postprocessing for SWI creation was described previously. Finally, SWI was displayed with continuous slices of 12-mm thickness using minimum intensity projection.

MR imaging showed schizencephaly in the right cerebral hemisphere, with findings of connection of the subarachnoid space to the lateral ventricle. The superficial parenchymal layer of the region of schizencephaly showed isointense compared to the cerebral cortex (Fig. 1A, B, D). SWI showed signal loss in the peripheral portion of the schizencephaly as well as at the intraparenchymal area, indicating previous hemorrhages. In addition, SWI showed tortuosity of the deep veins and the cortical veins because of the enhancing magnetic susceptibility effect of deoxyhemoglobin in the veins. In this case, SWI showed tortuosity of the deep veins and the cortical veins (Fig. 1C). MR angiography showed slight narrowing of the right middle cerebral artery but no abnormalities in other intracranial arteries (Fig. 1D).

Because of the presence of schizencephaly and intracranial hemorrhages, COL4A1 was sequenced, and a de novo mutation, c.3976G>A (p.G1326R), was identified as previously described.

**Discussion**

We found a peripheral hemorrhage in the region of the brain showing schizencephaly, intraparenchymal hemorrhages, and tortuosity of the veins on SWI in a child with a COL4A1 mutation. Intracranial hemorrhages are frequently seen in patients with COL4A1 mutations, probably attributable to the fragility of vessels that rupture either spontaneously or under specific conditions, such as trauma. SWI is a sensitive method for visualizing hemorrhages because of the enhanced magnetic susceptibility effect of hemoglobin and hemosiderin. Previous investigators have shown that SWI is more sensitive than conventional MR imaging sequences or CT for detecting foci of hemorrhages. In this case, SWI detected more foci of hemorrhages than conventional sequences. Because conventional MR imaging showed faint signal changes at the corresponding locations of the foci of the hemorrhage without parenchymal edema, the foci of the hemorrhage may be chronic. Previously reported hemorrhages on conventional MR imaging in patients with COL4A1 mutations include hemorrhages in the basal ganglia, periventricular white matter, and intraventricle as well as microbleeds in the internal capsule, midbrain, and cerebellum. More foci of hemorrhages can be detected if SWI is used in patients with COL4A1 mutations.

Intracranial hemorrhages during the antenatal or neonatal period are thought to result in porencephaly in infants with COL4A1 mutations. In addition, schizencephaly is associated with COL4A1 mutations. Schizencephaly is a type of brain malformation in which gray matter-lined clefts extend through the entire cerebral mantle, from the lateral ventricles to the cortex. Although the causes of schizencephaly may include vascular disruptions, prenatal infection, and genetic causes, vascular disruption is considered to be the main cause of schizencephaly. Because SWI showed foci of the hemorrhages in the peripheral portion of the region of schizencephaly as well as in the intraparenchymal area, indicating previous hemorrhages in this case, we assumed an association between a bleeding tendency and the occurrence of schizencephaly in this child. As Yoneda and associates suggested, the occurrence of schizencephaly and porencephaly may depend on the time of insult. Moreover, infants with severe encephaloclastic lesions that mimic hydrancephaly have been reported. Therefore, various brain parenchymal abnormalities may occur depending on the timing, degree, and location of the antenatal hemorrhage in patients with COL4A1 mutations.

SWI is also useful for demonstrating intracranial veins because of the enhancing magnetic susceptibility effect of deoxyhemoglobin in the veins. In this case, SWI showed tortuosity of the cortical and deep veins. Meeuwissen’s group reported tortuosity of vessels on a conventional image. To our knowledge, however, venous findings on SWI in patients with COL4A1 mutations have not been reported. More detailed visualization of the intracranial venous system can be obtained with SWI than with conventional MR imaging. Other than in the intracranial region, tortuosity is known to occur in the retinal arterioles in patients with COL4A1 mutations. Vessel tortuosity may be a characteristic finding in patients with COL4A1 mutations. Other
reported vessel lesions include multiple intracranial aneurysms\textsuperscript{11} and coronary stenosis.\textsuperscript{12} Furthermore, leukoencephalopathy in patients with \textit{COL4A1} mutations is thought to be caused by vessel angiopathy.\textsuperscript{11}

Symptoms in patients with \textit{COL4A1} mutations vary and are nonspecific, with onset starting at antenatal periods to late adulthood.\textsuperscript{1,6} Thus, this type of mutation is not always suspected clinically. Because no effective treatment has been established, reducing the chance of further hemorrhages by preventing trauma, avoiding intensive exercise, and
using anticoagulants is important. Moreover, patients with this mutation should be followed systemically because ocular and renal lesions may also be present.\(^1\) We believe that SWI findings are helpful for considering a possible association between intracranial MR imaging findings and \(COL4A1\) mutations.

In conclusion, we present SWI findings showing hemorrhages in the peripheral portion of the region of schizencephaly, intraparenchymal hemorrhages, and tortuosity of the veins. These findings may be helpful when considering the possible relationship between schizencephaly and \(COL4A1\) mutations.

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