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A severe pulmonary complication in a patient with *COL4A1*-related disorder: A case report

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ABSTRACT

Patients with *COL4A1* mutation-related disorders demonstrate a variety of disease phenotypes, which caused by small-vessel dysfunction in the brain, eyes, kidney, muscle, or heart. The involvement of organs mainly depends on the expression of the *COL4A1* gene. Complication or dysfunction of the alveolar tissue has not been reported in the literature *on COL4A1* mutation-related disorders. We herein report the case of a boy with schizencephaly, renovascular hypertension, and retinal arteriosclerosis of unknown origin, who suffered from severe and repetitive alveolar hemorrhage at 9 years of age. A novel *COL4A1* mutation was finally identified as the genetic cause. The pulmonary complication in the present case represents an important pathophysiological mechanism *COL4A1* mutation-related disorders; lung tissue with *COL4A1* gene mutations may be vulnerable and environmental substances and microorganisms in the air could accumulate to cause chronic damage in the alveolar tissues, especially in patients with tracheostoma and renovascular hypertension.

1. Introduction

Patients with *COL4A1* mutation-related disorders show a variety of phenotypes caused by small-vessel dysfunction in particular organs, such as brain (porencephaly, periventricular leukoencephalopathy, lacunar infarcts, dilated perivascular spaces, and micro- or deep-intracerebral hemorrhages, or cerebral aneurysms), eyes (congenital cataracts, retinal arterial tortuosity, eye anterior segment anomaly of Axenfeld-Rieger type), kidney (renal failure, renal cysts, renovascular hypertension, renal atrophy), muscle (cramps, myopathy), or the heart (arrhythmias). The specific organ involvement presumably depends on the expression of the *COL4A1* gene. *COL4A1* is an α1 component of a heterotrimer (α1α1α2), which is ubiquitously expressed in embryos and specifically in the vascular base membranes of particular organs during the lifetime. In addition, basal membranes with functionally specialized tissues, such as the brain, kidney, cochlea, eyes, and muscles, are correspondingly affected in patients with *COL4A1* mutation-related disorders. According to a recent report, type IV collagen in the basement membrane of the lung also plays fundamental roles in the coordination of alveolar morphogenesis, and the formation of the epithelium and vasculature [Jones et al., 2016]. To the best our knowledge, however, complication or dysfunction of the alveolar tissue has not been reported in the previous papers or review articles on *COL4A1* mutation-related disorders.

We herein report the case of a boy with schizencephaly, renovascular hypertension, and retinal arteriosclerosis of unknown origin, who suffered from severe and repetitive alveolar hemorrhage at 9 years of age, and in whom a novel *COL4A1* mutation was

Abbreviations: HANAC syndrome, Hereditary Angiopathy, Nephropathy, Aneurysms and muscle Cramps syndrome; CNS, central nervous system; MRI, magnetic resonance imaging; CT, computed tomography; ANCA, anti-neutrophil cytoplasmic antibody.

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finally identified as the genetic cause.

2. Clinical report

The patient was the first child of non-consanguineous parents with no family history of inherited disorders. A fetal ultrasound examination in a routine check-up detected ventricular dilatation in the fetal brain. The pregnant mother was therefore carefully followed up. The baby was delivered at term via a normal spontaneous delivery, but with neonatal asphyxia with an Apgar score of 6 and 9 at 1 and 5 min after birth, respectively. He was immediately transferred to the neonatal intensive care unit to treat generalized cyanosis, persistent hypoglycemia and hyperbilirubinemia. His birth weight was 2915 g and no major malformations were detected, with the exception of a cleft in the soft palate. Brain magnetic resonance imaging (MRI) at 28 days of age showed multiple cerebral hemorrhages and schizencephaly (Fig. 1A and B). He then showed marked growth and developmental delay and developed symptomatic West syndrome at 3 months of age. Permanent tracheostomy for his laryngomalacia was performed at 1 year of age. Subclinical hypertension was noticed at 3 years of age, and the presence of renovascular hypertension was identified based on the elevation of the plasma renin activity by Captopril; however, no apparent stenosis was detected in either of the renal arteries. An oral calcium channel blocker was administered but seemed less effective. At 8 years of age, an ophthalmological examination identified the presence of retinal arteriosclerosis. From 9 years of age, the patient repeatedly suffered from massive hemorrhage from the tracheostoma. Chest X-rays and CT revealed ipsilateral ground-glass opacity and interlobular septal thickening, indicating diffuse pulmonary hemorrhage (Fig. 1 C). Thrombocytopenia, coagulation abnormalities, and autoantibodies (including anti-neutrophil cytoplasmic antibody [ANCA]) were not detected. Hemosiderin-laden macrophages, a marker of idiopathic pulmonary hemosiderosis, were not observed in bronchoalveolar lavage or gastric fluid specimens. We hypothesized that the patient had an underlying genetic disease that was associated with vascular vulnerability.

We performed whole exome sequencing as previously described [Fukai et al., 2016] and found a novel heterozygous mutation of the *COL4A1* gene (Fig. 2, NM_001845.5 c.3104G > T [p.Gly1035Val]). This mutation was confirmed by a conventional PCR and direct sequencing with a following primer set: forward: 5′-ttcatttgtaataccagcactagc-3'; reverse: 5′-ctccactgagctgggagaa-3'. The mutation cause substitution of a highly conserved Gly residue in the Gly-X-Y repeat, suggesting that the mutation is very likely to be pathogenic as reported previously [Yoneda et al., 2013]. We also assessed the pathogenicity of this mutation using a Poly-Phen2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) with the score of 1.00, “Probably Damaging”, suggesting that this novel mutation has high pathogenicity.

At 11 years of age, 2 years after the first episode of pulmonary bleeding, the patient died of hemorrhagic shock due to massive bleeding from the tracheo-innominate artery fistula.

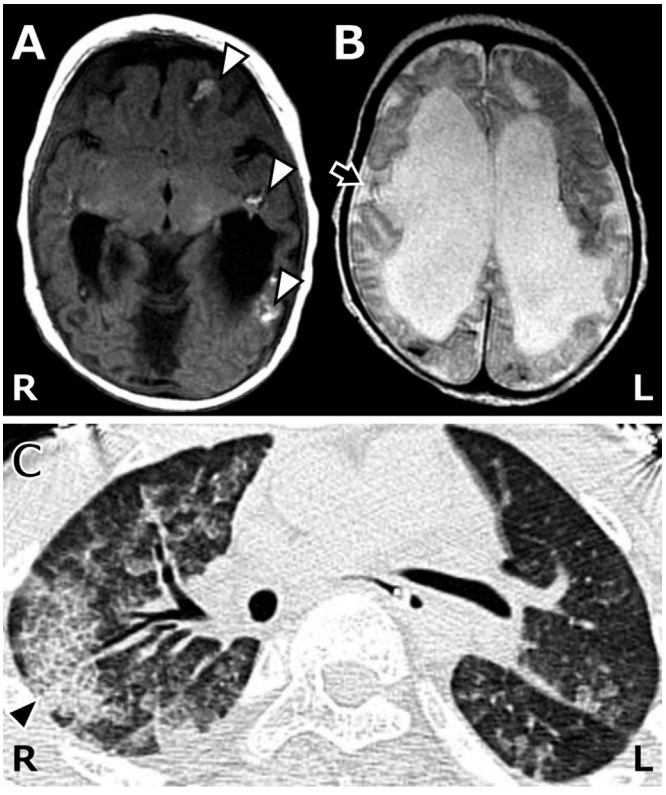

Fig. 1. The clinical images of the patient.
Brain MRI at 1 month of age showed multiple hemorrhage (white arrowheads) and open-lip schizencephaly (black arrow). A) T1-weighted imaging; B) A T2-weighted imaging.
C) Alveolar hemorrhage at 9 years of age. A chest CT scan showed ipsilateral ground-glass opacity and interlobular septal thickening (black arrowhead). R: right, L: left.

3. Discussion

The initial cases of *COL4A1* mutation-related disorders were reported in patients with familial porencephaly (OMIM 175780) or cerebral micro-angiopathy (OMIM 607595) [Debus et al., 2004; Gould et al., 2006] and patients with hereditary angiopathy, nephropathy, aneurysms and muscle cramps (HANAC; OMIM 611773) syndrome [Gould et al., 2005; Plaisier et al., 2007; Sibon et al., 2007]. Then, *COL4A1* mutations have been reported to be causative for cobblestone lissencephaly or schizencephaly [Labelle-Dumais et al., 2011; Yoneda et al., 2013]. According to a recent review, patients harboring *COL4A1* mutation present diverse clinical symptoms, such as recurrent bleeding or congenital vascular abnormalities of the central nervous system (CNS), kidney, ear, and eye [Kuo et al., 2012]. To the best of our knowledge, alveolar hemorrhage has only been reported in patients with Goodpasture syndrome, an autoimmune collagen-IV related disease.

In most cases, the organ specificity would probably be based on the expression of the *COL4A1* gene in combination with secondary damage from environmental factors. Our patient represents the reported case of *COL4A1*-related disease with alveolar hemorrhage. We consider the pathophysiology of the lung-specific disease in this 9-year-old boy. First, the alveolar tissue, especially the basal membranes in capillaries, of patients with *COL4A1* gene mutations may be vulnerable in nature and various environmental substances and microorganisms in the air could cause chronic damage. Second,

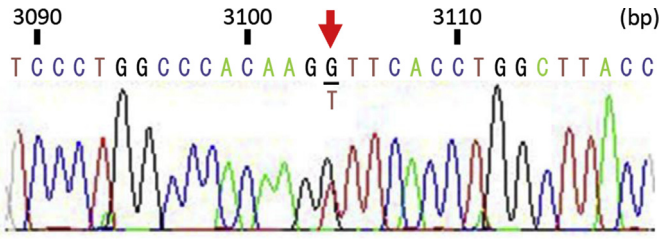

Fig. 2. The analysis of the *COL4A1* gene.
An arrow indicates a novel heterozygous mutation of the *COL4A1* gene, c.3104G > T (p.Gly1035Val).

early tracheostomy to treat the patient's upper airway obstruction would have endangered the lungs by directly exposing them to open air and infective agents. Third, the patient's intractable renovascular hypertension, which is highly associated with *COL4A1*-related disease, might have exacerbated the damage of the alveolar tissues.

In conclusion, pulmonary complications should be considered in patients with *COL4A1* mutation-related disorders. A further investigation should be performed to investigate how alveolar damage proceeds with time and when pulmonary complications become evident. A study with a larger patient population and a well-planned protocol will reveal the risk of pulmonary complications in patients with *COL4A1*-related disease.

Disclosure

The authors declare no conflicts of interest in association with the present study.

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