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

Yoshiichi Abe, Atsuko Matsuduka, Kazuo Okanari, Hiroaki Miyahara, Mitsuhiro Kato, Satoko Miyatake, Hirotomo Saito, Naomichi Matsumoto, Maeda Tomoki, Kenji Ihara*

*Department of Pediatrics, Oita University Faculty of Medicine, Yufu-City, Oita, Japan
bDepartment of Pediatrics, Beppu Developmental Medicine and Rehabilitation Center for Children with Mental Retardation and Motor Disabilities, Beppu-City, Oita, Japan
cDepartment of Pediatrics, Showa University School of Medicine, Tokyo, Japan
dDepartment of Biochemistry, Hamamatsu University School of Medicine, Hamamatsu-City, Shizuoka, Japan
eDepartment of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan

ABSTRACT

Patients with COL4A1 mutation-related disorders demonstrate a variety of disease phenotypes, which caused by small-vessel dysfunction in particular organs, such as brain (porencephaly, periventricular leukoencephalopathy), kidney (renal failure, cysts, renovascular hypertension), 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 basement membrane 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 of 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 identified as the genetic cause. The pulmonary complication in the present case represents an important pathophysiological mechanism of 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.

© 2016 Elsevier Masson SAS. All rights reserved.
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 dilation 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 cerebrohemorrhages 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 cytoplasmatic 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'-ttcatttgtaa-taccacagtacgc-3'; reverse: 5'-tctccagtacgctggagaag-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.

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 cobblesone 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,
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.

Acknowledgements

We would like to express our gratitude to the patient and family for their cooperation.

We thank Dr. Brian Quinn for his support.

References


