Case Report

A Neonatal Patient Diagnosed with a COL4A1 Mutation Presenting with Hemorrhagic Infarction and Severe Jaundice

Akihiro Kirimura, Hajime Yasuhara, Soshi Hachisuka, Kumiko Takagi, Reiko Ebisu, Ayako Ohgitani, and Hideki Minowa

Department of Neonatal Intensive Care Unit, Nara Prefecture General Medical Center, Nara, Japan

Correspondence should be addressed to Akihiro Kirimura; akirimura0614@nara-hp.jp

Received 7 May 2022; Accepted 5 September 2022; Published 14 October 2022

Academic Editor: Balraj Mittal

Copyright © 2022 Akihiro Kirimura et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We report a patient diagnosed with a COL4A1 mutation in the early postnatal period. Patients with early postnatal jaundice, intracranial lesions that are negative for TORCH syndrome, and recurrent hemolytic anemia should be suspected of having a COL4A1/COL4A2 gene mutation.

1. Introduction

COL4A1 and COL4A2 are genes encoding molecular chains that are major components of type IV collagen, which is found in basement membranes throughout the human body. Mutations in the COL4A1 and COL4A2 genes are known to cause schizencephaly and porencephaly and have been increasingly reported in recent years. Mutations in the COL4A1 and COL4A2 genes cause a wide variety of symptoms in the cerebrovascular, renal, ocular, cardiac, and muscular regions and are referred to as COL4A1/COL4A2 mutation-related disorders [1].

We experienced a case of early jaundice requiring exchange transfusion and intracranial lesions suspicious for the TORCH syndrome, which led to an early diagnosis of a COL4A1 mutation. We report the clinical features of the case together with a discussion of the recent literature.

2. Case Report

The mother was a 23-year-old woman with 2 pregnancies and 1 delivery, a blood type of O/Rh plus, and no pregnancy complications. She had a spontaneous vaginal delivery at 39 weeks and 0 days gestation. The mother tested negative for syphilis, hepatitis B, hepatitis C, human immunodeficiency virus, chlamydia, and Group B Streptococcus. Her rubella antibodies were less than 8-fold. We did not screen for cytomegalovirus (CMV) and toxoplasma antibodies. The patient was a female infant with a birth weight of 2450 g (−1.56 SD) and a head circumference of 28.5 cm (−3.41 SD) with Apgar scores of 8 (1-minute score) and 9 (5-minute score). Due to unstable oxygen saturation after birth, she was given oxygen at FiO2 0.3 in the incubator under observation, but on Day 1, her total bilirubin level rose to 13.2 mg/dL (225.7 μmol/L), her jaundice worsened, and she was transferred to our department on the same day.

At the time of admission, her general vitality was somewhat poor, and there were myoclonus-like involuntary movements of the limbs that were suspected to be irritant. She had a small head but did not show any disease-specific facial abnormalities. No other obvious external deformities were observed. Blood tests at the time of admission showed an elevated level of CK (4050 U/L) and hyperbilirubinemia (13.7 mg/dL [234.3 μmol/L]). On admission, head ultrasonography showed marked enlargement of the left ventricle and hyperintense areas in the bilateral thalamus, and a simple brain CT was performed on the same day, which showed bilateral ventricular enlargement with left-sided predominance, periventricular calcification, and ischemic changes (Figure 1).
Initially, we suspected jaundice due to ABO blood group incompatibility. Phototherapy was started on Day 1, and intravenous immunoglobulin was administered, but the total bilirubin level rose to 15.2 mg/dL (259.9 μmol/L), so an exchange transfusion was performed on the same day. After Day 2, the total bilirubin level gradually decreased, and phototherapy was completed on Day 7. Her blood type was A Rh plus, and anti-A antibodies derived from maternal blood were observed, but the diagnostic criteria for ABO blood group incompatibility were not met, as anti-A antibodies were 128-fold (<512-fold) in maternal serum and 4-fold (<8-fold) in the patient’s serum.

For the intracranial lesion, the TORCH syndrome was suspected, but the patient’s CMV-IgM antibody, Toxoplasma IgM antibody, and herpes simplex virus IgM tests were all negative. In addition, a real-time PCR test using the infant’s urine was also negative for CMV DNA. There were no pathological abnormalities in coagulation and hemostatic function, and protein C and protein S activities were not significantly decreased. An electroencephalogram (EEG) performed on Day 3 showed reproducible sharp waves in the left hemisphere and slow wave rhythms in the bilateral occipital regions, which suggested epilepsy. A simple brain MRI was performed on Day 10 and showed multiple hemorrhagic infarcts with intraventricular perforation and cerebellar atrophy (Figure 2). Rhythmic myoclonus-like seizures appeared on Day 23, and she was started on oral phenobarbital. Simple brain MRI was performed on Day 25 and did not reveal any new lesions.

She developed anemia (Hb 9.1 g/dL) on Day 18 and was started on oral iron and subcutaneous erythropoietin. However, her Hb level decreased to 6.1 g/dL by Day 29, and red blood cell transfusion was performed by Day 30. After the transfusion, her Hb level remained in the 910 g/dL range, and her seizures were well controlled, so she was discharged on Day 39. After discharge, the anemia worsened again to a Hb level of 6.7 g/dL on Day 53, and she was hospitalized on Day 54 and underwent a second red blood cell transfusion. Since then, there has been no recurrence of anemia requiring a red blood cell transfusion.

We suspected a COL4A1/COL4A2 mutation as the cause of the early jaundice and perinatal hemorrhagic infarction, and with the consent of her parents, we performed a genetic investigation of the patient using next generation sequencing and identified a heterozygous missense mutation in the COL4A1 gene (p. Gly586Asp, chr13: 11018625). Although this is a novel variant that is not registered in the ClinVar database, it is a glycine substitution in the triple helix domain, which is the most frequent cause of porencephaly and schizencephaly in the previous reports and is considered to be a pathological variant. Therefore, we diagnosed the patient with COL4A1-related syndrome. We also examined the parents’ genes and found no abnormalities in the COL4A1 gene, indicating that the mutation was de novo.

At present, she is 10 months old. Her elevated level of CK has improved, and there has been no sign of recurrence of jaundice or anemia requiring a red blood cell transfusion, but she has persistent intractable seizures and developed hypsarrhythmia shown on EEG at 6 months of age. She was diagnosed with West syndrome and is being managed with multiple antiepileptic drugs and ACTH therapy. She is still not cervically stable and is developmentally delayed. Although COL4A1-related syndromes are known to cause cardiac, renal, and ocular abnormalities, she had no obvious complications on echocardiography, abdominal ultrasound, or ophthalmologic examination.

3. Discussion

In this case, the following features led to the early diagnosis of COL4A1/COL4A2-related syndromes: (1) intracranial lesions suggestive of the TORCH syndrome were found at birth, but all related tests were negative; (2) severe hemolytic jaundice could not be explained by ABO incompatibility; and (3) the progression of anemia requiring a blood transfusion despite standard treatment.

Gould et al. found COL4A1 mutations in humans and mouse familial porencephaly, and validation in mice showed that mutations in the COL4A1 gene cause vascular fragility leading to cerebral hemorrhage and porencephaly [2, 3]. COL4A2 has a low penetrance of mutations, which makes linkage analysis difficult. However, COL4A2 mutations have recently been confirmed to cause cerebral hemorrhage as well [4, 5]. Cerebral hemorrhage during fetal life causes damage to the neural tissue, resulting in schizencephaly or porencephaly at birth. Both schizencephaly and porencephaly can lead to a variety of neurological symptoms, such as cerebral palsy, mental retardation, and epilepsy, after birth. The mechanism causing cerebral hemorrhage in COL4A1/COL4A2-related syndromes has not yet been explored, but it is thought to be caused by a combination of genetic factors, such as mutations in the α1 chain of type IV collagen, which impair the stability of basement membranes and weaken the cerebral vascular tissue, and environmental factors, such as pressure and trauma associated with delivery [2, 3]. Tomotaki et al. reported that 15 (21%) of 61 patients
with porencephaly and 10 patients with schizencephaly had
\textit{COL4A1} mutations (5 of which were de novo mutations) [6].
Meuwissen et al. performed genetic examinations of 183
patients with cerebral hemorrhage or porencephaly and their
parents and identified \textit{COL4A1} and \textit{COL4A2} mutations in
24 patients (13%) (21 \textit{COL4A1} mutations and 3 \textit{COL4A2}
mutations, including 10 de novo mutations) [1]. The
pathogenesis of hemolytic anemia in the neonatal period has
not yet been explored, but it is thought that the dysfunction
of basement membranes leads to the destruction of red
blood cells via the vascular system and reticuloendothelial
system [7]. In most of the reported cases, anemia tends to
improve within the first few months after birth. This is
thought to be related to the development and maturation of
the skeletal and nonskeletal components of erythrocytes.
Mentzer et al. showed that free 2,3-diphosphoglycerate (2,3-
DPG), present in neonatal erythrocytes, causes severe me-
chanical fragility in the erythrocytes of infants with he-
reditary erythrocytosis [8]. The decrease in free 2,3-DPG
associated with the transition from fetal hemoglobin to adult
hemoglobin results in a reduction in hemolytic anemia, and
the same mechanism may explain the course of hemolytic
anemia in \textit{COL4A1/COL4A2}-related syndromes.

There is no fundamental treatment for \textit{COL4A1/COL4A2}-
related syndromes, and only symptomatic treatment with
antiepileptic drugs and rehabilitation is available for epilepsy
and psychomotor retardation caused by damage to the brain
tissue. Our patient will also require extensive treatment for
neurological symptoms that may develop in the future, in
addition to her symptoms caused by West syndrome. On the
other hand, the identification of the \textit{COL4A1} mutation was a
great advantage for us in explaining the future condition and
treatment prospects to the family in detail.

4. Conclusion
Early postnatal jaundice, intracranial calcification, and
hemorrhagic infarction led us to identify the \textit{COL4A1}
mutation. Neurological symptoms and intracranial lesions
are not the only symptoms of these mutations, but jaundice
and recurrent hemolytic anemia can also lead to diagnosis in
the neonatal period.

It is necessary to suspect \textit{COL4A1/COL4A2}-related
syndromes in intracranial lesions that are negative for the
TORCH syndrome. In this case, identification of the gene
mutation was important for future prediction of the disease
and genetic counseling for the family.

Data Availability
Data sharing is not applicable to this article as no new data
were created or analyzed in this study.

Conflicts of Interest
The authors declare that they have no conflicts of interest
associated with this manuscript.

Authors’ Contributions
AK drafted the initial manuscript and prepared figures.
HY critically reviewed the manuscript and commented
on drafts of the manuscript. SH, KT, RE, and AO were
major contributors in writing the manuscript. HM
critically reviewed and revised the manuscript. All au-
thors contributed to the article and approved the sub-
mitted version.
References

[1] M. Meuwissen, D. Halley, L. S. Smit et al., “The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature,” *Genetics in Medicine*, vol. 17, pp. 843–853, 2015.

[2] D. B. Gould, F. C. Phalan, S. E. Mil et al., “Role of COL4A1 in small-vessel disease and hemorrhagic stroke,” *New England Journal of Medicine*, vol. 354, pp. 1489–1496, 2006.

[3] D. B. Gould, F. C. Phalan, G. J. Breedveld et al., “Mutations in COL4A1 cause perinatal cerebral hemorrhage and porencephaly,” *Science*, vol. 308, no. 5725, pp. 1167–1171, 2005.

[4] E. Verbeek, M. E. Meuwissen, F. W. Verheijen et al., “COL4A2 mutation associated with familial porencephaly and small-vessel disease,” *European Journal of Human Genetics*, vol. 20, no. 8, pp. 844–851, 2012.

[5] S. Koene, C. M. P. C. D. Peeters-Scholte, J. Knijnenburg et al., “Intracerebral hemorrhage in a neonate with an intragenic COL4A2 duplication,” *American Journal of Medical Genetics, Part A*, vol. 185, no. 2, pp. 571–574, 2021.

[6] S. Tomotaki, H. Mizumoto, T. Hamabata et al., “Severe hemolytic jaundice in a neonate with a novel COL4A1 mutation,” *Pediatrics & Neonatology*, vol. 57, no. 6, pp. 522–525, 2016.

[7] H. Ogura, S. Ohga, T. Aoki et al., “Novel COL4A1 mutations identified in infants with congenital hemolytic anemia in association with brain malformations,” *Human Genome Variation*, vol. 7, pp. 42–44, 2020.

[8] W. C. Mentzer, T. A. Iarocci, N. Mohandas et al., “Modulation of erythrocyte membrane mechanical stability by 2, 3-diphosphoglycerate in the neonatal poikilocytosis/elliptocytosis syndrome,” *Journal of Clinical Investigation*, vol. 79, no. 3, pp. 943–949, 1987.