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Clinical Observations

COL4A1 Mutation in a Neonate With Intrauterine Stroke and Anterior Segment Dysgenesis

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ABSTRACT

BACKGROUND: *COL4A1* on chromosome 13q34 encodes the alpha 1 chain of type IV collagen, a component of basal membranes. It is expressed mainly in the brain, muscles, kidneys, and eyes. *COL4A1* mutations can remain asymptomatic or cause devastating disease. Neonates and children may present with porencephaly, intracerebral hemorrhage, or hemiparesis, whereas adults tend to develop intracranial aneurysms or retinal arteriolar tortuosities. **PATIENT DESCRIPTION:** We describe a term infant with encephalomalacia, extensive intrauterine stroke and anterior segment dysgenesis with a *de novo* mutation in *COL4A1*. **CONCLUSIONS:** Identification of this mutation in affected individuals has implications for perinatal management and genetic counseling.

Keywords: fetal porencephaly, hemorrhagic stroke, cataract, Axenfeld–Rieger

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Introduction

COL4A1 on chromosome 13q34 encodes the alpha 1 chain of collagen type IV.[1] Type IV collagens are basement membrane proteins that are expressed in all tissues, including the vasculature. *COL4A1* plays an important role in the cohesiveness of the basement membrane, maintenance of vascular tone, and endothelial cell function.[2] Vascular defects caused by a semidominant mutation in *COL4A1* that inhibits the secretion of abnormal and normal type IV collagen were first shown in a mutant mouse model.[3] These animals exhibited severe perinatal cerebral hemorrhage and porencephaly secondary to focal disruptions of vascular basement membranes.[3] In addition, the mutant mice were smaller than controls and had multiple pleiotropic phenotypes including ocular and renal abnormalities and reduced fertility.[3] Thus, one of the main characteristics of individuals with a *COL4A1* mutation is the presence of a multisystemic phenotype, with variable involvement of the brain, eyes, kidneys, and muscles.[1,2] We present a newborn with a fluid-filled anterior fossa associated with loss of parietal, frontal, and temporal lobes on fetal magnetic resonance imaging (MRI) who was diagnosed postnatally with a *COL4A1* mutation.

Patient Description

This girl was born at 39 weeks' gestation to a 24-year-old Caucasian primigravida whose past medical history was notable for well-controlled asthma and obesity. At birth, she was small for gestational age (SGA)—weight and length less than the third percentile, and head circumference fifth percentile. Her mother had good prenatal care and her routine prenatal laboratory results were unremarkable. There was no known exposure to tobacco smoke, alcohol, drugs, or other toxins. The pregnancy was complicated only by type A1 gestational diabetes mellitus. Findings of an ultrasound at 16 weeks of gestation were normal. An ultrasound at 31 weeks of gestation, however, demonstrated decreased fetal size that was less than the third percentile. In addition, cranial imaging demonstrated

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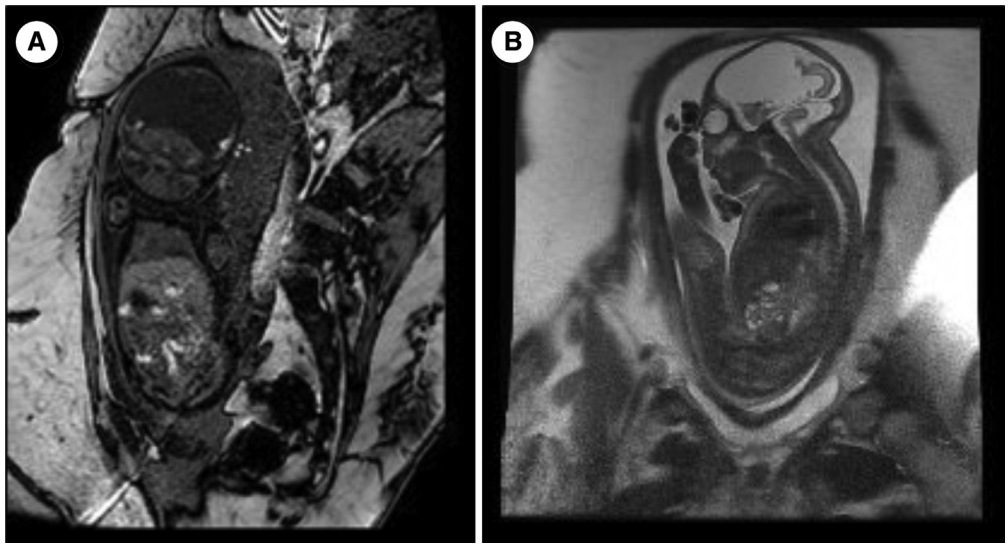

FIGURE 1.
Fetal MRI with coronal T1-weighted (A) and sagittal T2-weighted imaging (B) demonstrates an extensive intrauterine stroke with near complete loss of parietal lobes and majority of frontal and temporal lobes, involving both cortex and white matter.

fluid-filled frontal lobes, absent septum pellucidum and falx cerebri, and enlarged posterior horns of the lateral ventricles. The midline hypothalamus and posterior fossa appeared normal, although the cerebellum was consistent with that of a 24-week gestation fetus. A fetal MRI (Fig 1) at 32 weeks of gestation revealed near complete loss of parietal, frontal, and temporal cortices and white matter. There was a small detectable ribbon of cortex in the occipital lobes and no evidence of a third ventricle. The cerebellum was small with abnormal T2-weighted signal and small cysts. T1-weighted sequences suggested residual hemorrhagic products versus mineralization in the calvarium along the margins of the frontal lobes and in the dependent right cerebrum. Collectively, these findings suggested a previous infarction. The thalamus and brainstem were relatively preserved. In addition, the fetal MRI revealed that the globes of the eyes appeared long. The family declined amniocentesis. Instead, an extensive prenatal evaluation was performed including cell-free DNA for trisomy 13, 18, 21, monosomy X, 22q11.2 deletion, and platelet reactivity testing, which were all negative. No family members had experienced birth defects, eye abnormalities, genetic diseases, intellectual disability, or learning disorders. There was no history of frequent miscarriages, bleeding disorders, infertility, infant or childhood deaths, or known familial disorders. The father reported a history of migraines and the mother had a history of headaches along with a distant family history of stroke.

The infant was delivered via Cesarean section for breech presentation. She had intact respiratory drive and required minimal oxygen support. Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. Pertinent findings on examination revealed that the she was SGA and had eye abnormalities including eyelid edema, proptosis, minimal visibility of the sclera, cloudy cornea, absent red reflexes, and bilateral size and shape abnormalities of the pupil and iris (Fig 2). Ophthalmologic examination suggested anterior segment dysgenesis. This included complete malformation of the cornea, anterior chamber, and trabecular meshwork and iris. She also exhibited megalocornea, bilateral absence of lens, and increased intraocular pressures. Postnatal MRI of the brain showed little parenchyma in the distribution of the middle, anterior, and posterior cerebral arteries bilaterally, suggesting hemorrhagic infarction in those territories with cystic encephalomalacia (Fig 3). There was mass effect on the brainstem with cerebral aqueductal obstruction and cervical medullary kinking. Encephalomalacia and hemorrhagic debris were seen in the cerebellar hemispheres, suggesting cerebellar hemorrhagic infarctions. Bilateral globe abnormalities were also visualized.

The postnatal evaluation included testing of coagulation factors and microarray. In addition, based on the patient's clinical features, sequencing on *COL4A1* was submitted. The hospital course was uneventful and she was discharged taking full oral feeds. After discharge, results of the testing demonstrated a point mutation at Gly785Glu on the *COL4A1* gene. On subsequent follow-up visits, she exhibited severe developmental delay and visual impairments. At age 4 months, she presented to the physician's office with irritability and a rapidly increasing head circumference was demonstrated. The infant was subsequently admitted to the hospital for concerns of obstructive hydrocephalus, and a ventriculoperitoneal shunt was placed. Both the mother and father were negative for the single site *COL4A1* point mutation. Thus the risk for the parents to have another child in the future with the same mutation is less than 1%.

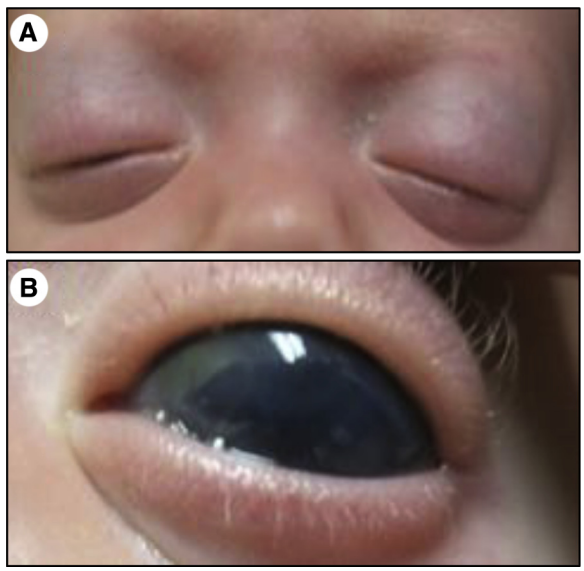

FIGURE 2.
Eye examination demonstrates eyelid edema and proptosis (A) and minimal visibility of the sclera, cloudy cornea, and abnormal size and shape of the pupil and iris (B). (The color version of this figure is available in the online edition.)

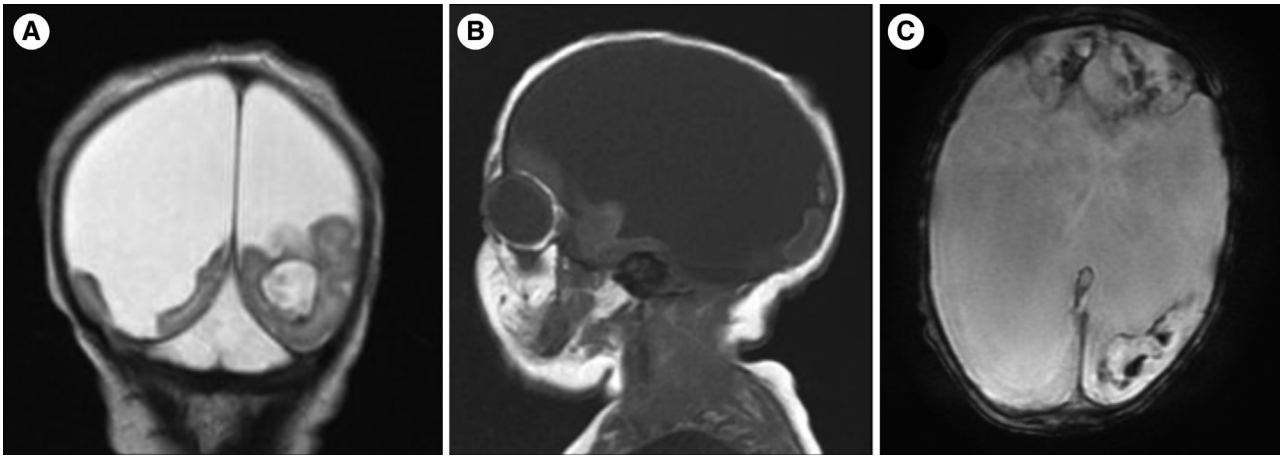

FIGURE 3.
Noncontrast brain MRI with coronal fast spin echo T2-weighted (A) and sagittal T1-weighted (B) imaging demonstrate severe cystic encephalomalacia and minimal residual brain parenchyma. Susceptibility weighted imaging (C) suggests evidence of hemorrhagic infarcts.

Discussion

Our patient's presentation, consisting of cystic encephalomalacia likely caused by significant intrauterine bilateral hemorrhagic infarctions and anterior segment eye anomalies, was consistent with a *COL4A1* mutation. *COL4A1*-related disorders involve a wide spectrum of clinical symptoms that can include the brain, ocular, renal, and muscle involvement, as well as reports of Raynaud phenomenon and supraventricular arrhythmia.[1,4] Brain dysfunction can manifest as hemiplegia, migraine, seizures, dementia, intellectual disability, intracerebral hemorrhage, and ischemic stroke.[5] Intracerebral hemorrhage can occur at any age, including antenatally.[6-10] There is, in addition, the potential for recurrent episodes. Neuroimaging can demonstrate porencephaly characterized by a fluid-filled cavity, leukoencephalopathy, cerebral microhemorrhages, lacunar infarcts, deep intracerebral hemorrhages, dilated perivascular spaces, and intracranial aneurysms.[2,3,11] Multiple ophthalmologic findings have been described, including bilateral tortuosity of the second- and third-order arteries, hemorrhagic lesions, and the Axenfeld–Rieger anomaly characterized by microcornea, congenital or juvenile cataract, increased intraocular pressure, iris hypoplasia, retinal detachment, and optic nerve excavation.[12,13] Renal involvement manifests as hematuria and renal cysts.[13] Muscle cramps involving a variety of muscles have been reported with associated persistent elevation of serum creatine kinase concentrations.[13]

COL4A1 mutations are inherited as an autosomal dominant trait with near 100% penetrance and variable expression depending of the age of onset and severity of clinical symptoms, even within the same family. Therefore, if a parent of the proband is affected, the risk to the siblings is 50%. There may also be *de novo* mutations or low-level parental mosaicism. However, the proportion of these individuals in the population is unknown.

As illustrated by our patient, and others,[7-10] the clinical onset of brain small-vessel disease due to *COL4A1* mutations can occur even in the antenatal period. Patients diagnosed with stroke, both *in utero* and postnatally, often do not have an obvious etiology. Therefore, a detailed family history and ophthalmologic examination may be warranted to identify other small-vessel organ involvement, as *COL4A1* mutations may be underestimated in this population. In one series, three of the four neonates with extensive prenatal porencephaly had no family history but experienced sporadic *COL4A1* mutations.[10]

Identification of a *COL4A1* mutation has significant implications. Prenatal testing can be performed by chorionic villus sampling or by amniocentesis if one of the parents is known to carry the mutation. Preimplantation genetic diagnosis may also be an option for these families. Furthermore, preventive measures, such as Cesarean delivery, could be performed in individuals whose family is known to harbor a *COL4A1* mutation.

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