Fetal Origin of Brain Damage in 2 Infants with a *COL4A1* Mutation: Fetal and Neonatal MRI

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- fetal intracerebral hemorrhage
- porencephaly
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Abstract

Mutations in the gene COL4A1, encoding collagen IV A1, are associated with familial porencephaly. Previously, COL4A1 mutation-associated antenatal hemorrhages have been suggested by early post-natal imaging. We describe 2 children with fetal intracerebral hemorrhages and a COL4A1 mutation. There was also extensive hemispheric tissue loss in both infants and loss of cerebellar tissue in one infant. This paper show prenatal evidence of fetal hemorrhage in association with a COL4A1 mutation.

Introduction

Mutations in the gene COL4A1, encoding collagen IV A1, are associated with familial porencephaly [2, 3, 7]. COL4A1 mutations lead to change of the basal membrane of capillaries, resulting in microangiopathy [3]. In the brain the microangiopathy may not only lead to hemorrhage around birth, but also to a progressive leukoencephalopathy, infarcts and micro- as well as macrobleeds in the cerebral hemispheres, brain stem and cerebellum [3]. The phenotype of familial porencephaly typically also includes cataract and, less frequently, nephropathy [4]. Intracerebral hemorrhages in premature infants may be caused by a COL4A1 mutation, but only in exceptional cases [1]. Most all evidence for an antenatal origin of the intracerebral hemorrhage has been demonstrated indirectly through postnatal imaging. In this study we describe 2 infants with a COL4A1 mutation and fetal intracerebral hemorrhages with posthemorrhagic ventricular dilatation on their fetal MRI.

Materials and Methods

Patients

The pregnancy of infant A was uncomplicated until 28 weeks gestation. Fetal ultrasound at that time showed asymmetrical loss of cerebral tissue and widening of the lateral ventricles. Fetal single-shot T_2-weighted images at 29 4/7 weeks gestation showed dilated lateral ventricles, a focal cerebral mantle defect in the left parietal region and an intraventricular hemorrhage on the left (**Fig. 1a, b**). He was prematurely born at 31 1/7 weeks gestation. Within the first week he developed an additional hemorrhage in the basal nuclei on the right (**Fig. 1c**). He subsequently developed a severe posthemorrhagic hydrocephalus. He had neonatal seizures. A heterozygous c.2245G>A mutation was found in COL4A1. This mutation leads to glycine-to-serine substitution at protein level (p.Gly749Ser). Because of the poor clinical condition, the rapid postnatal deterioration and the risk of inducing further hemorrhages the hydrocephalus was not shunted. He died at the age of 10 months. At that time he had lost most cerebral tissue (**Fig. 1d**). We found the same mutation in the COL4A1 in the father of the patient. He had only minor white matter abnormalities on MRI (data not shown).

The pregnancy of the infant B was uncomplicated until 37 weeks gestation. Because of suspected fetal growth retardation a fetal ultrasound investigation was performed. The ultrasound investigation showed a decreased biparietal distance and head circumference (<p5) with a slightly enlarged ventricles. Fetal single-shot T_2-weighted images at 38 2/7 weeks gestation showed a dilated ventricular system with bilateral focal areas of cerebral tissue loss and an intraventricular hemorrhage (**Fig. 1e, f**). The child was born at 40 weeks gestation. She developed seizures in the neonatal period. Brain MRI at the age of 1 month showed dilated lateral ventricles and cerebral tissue loss in the right occipital and left

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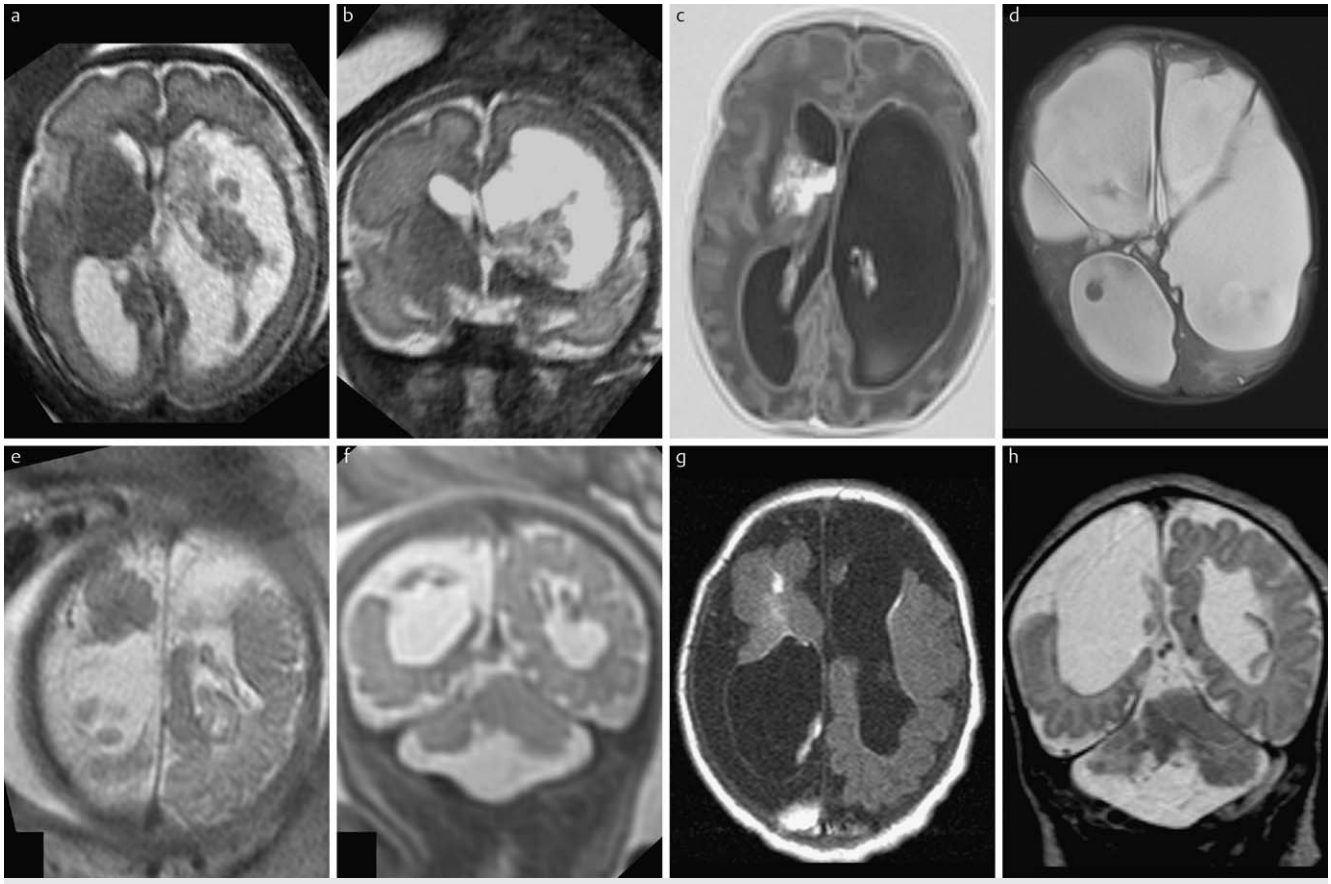

Fig. 1 Patient A – Fetal single-shot T_2-weighted images at 35 weeks gestation; (**a**) transverse plane and (**b**) a coronal plane, showing the remains of a left intraventricular hemorrhage with widening of the left lateral ventricle and loss of the surrounding tissue (i. e., porencephaly). Postnatal MR images: (**c**) transverse Inversion recovery MR image (age 1 week) showing the pre-existent left intraventricular hemorrhage and a new hemorrhage in the basal nuclei on the right and (**d**) a single-shot T_2-weighted image at the age of 3 months showing severe bilateral hydrocephalus. Patient B – Fetal single-shot T_2-weighted images at 38 2/7 weeks gestation; (**e**) transverse plane and (**f**) coronal plane, showing asymmetric loss of cortex, white matter and cerebellum and intraventricular hemorrhage. Postnatal MR images at 1 month; (**g**) transverse T_1-weighted image showing loss of white matter and cortical tissue right parietal-occipital and left frontal regions with high signal intensity probably due to remnants of haemorrhage and (**h**) coronal T_2-weighted MR image showing complete loss of right parietal and hemorrhagic infarction of the right cerebellar hemisphere.

frontal regions. The basal ganglia and the right cerebellar hemisphere were also affected (▶ **Fig. 1g, h**). At the age of 4 months her seizures became therapy resistant. She still has numerous seizures daily, with a lack of any psychomotor development. A heterozygous c.4150G > A mutation was found in the COL4A1 gene. This mutation leads to glycine-to-serine substitution at protein level (p.Gly1384Ser). We did not find the mutation in the parents of this patient.

Discussion

In this report we demonstrate the fetal origin of the intracerebral hemorrhages and brain tissue atrophy and ventriculomegaly in 2 infants with a COL4A1 mutation. Previously, de Vries et al. showed progressive cerebral damage in 2 prematurely born infants with a COL4A1 mutation and suggested antenatal onset, because neuroimaging was performed immediately after birth [2]. Very recently, this group also showed cerebral damage of antenatal onset [8].

Gould and coworkers found severe cerebral damage in heterozygous mutant COL4A1 mice pups and suggested that Caesarean section could prevent brain damage [3]. Our antenatal MRIs are the first direct human evidence that a COL4A1 mutation can result in major intracerebral hemorrhages and infarction before birth.

Familial porencephaly is the most typical presentation of a COL4A1 mutation [3]. Other patients may present with leukoencephalopathy, ischemic infarcts and hemorrhages later in life [5,6]. More recently, the phenotype of COL4A1 mutations was extended with hereditary angiopathy, nephropathy, aneurysms, and muscle cramps [4].

We suggest that COL4A1 mutational analysis should be considered in infants, both premature and term born, with a history of fetal intracerebral hemorrhage or an unexplained postnatal progressive intracerebral hemorrhage or ischemia.

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