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Brain Pathology

CASE IMAGE

Under Your Microscope

# An 18-month-old with white matter calcifications and seizures

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## 1 | CLINICAL HISTORY

The patient was born at 41 weeks gestation by normal spontaneous vaginal delivery (NSVD) after an uneventful pregnancy to a 27-year-old primigravid woman. She progressed through appropriate developmental milestones until 3.5 months, when she experienced two generalized seizures at home and a similar seizure in the community hospital emergency room. An MRI revealed partial corpus callosum agenesis, a communicating interhemispheric cyst, and abnormal gyral patterns in the right peri-sylvian and left frontal para-sagittal cortex (Figure 1). EEG demonstrated markedly abnormal asymmetry, with mildly attenuated right hemisphere function

**BOX 1 Slide scan**

Access the whole slide scan at https://image.upmc.edu:8080/NeuroPathology/BPA/BPA-22-01-002/view.apml?

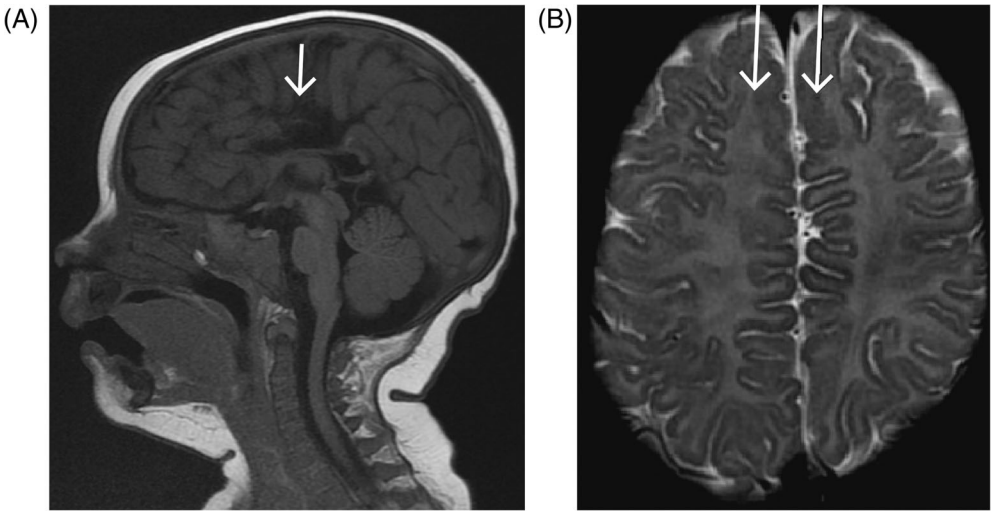


FIGURE 1 MRI performed at 4 months of age. (A) Agenesis of the corpus callosum and malformation of the cingulate gyrus (arrow) on a T1 weighted MRI. (B) Abnormal gyration, bilateral medial frontal lobes (arrows), compared with normal gyral pattern posteriorly and laterally on a T2 weighted MRI axial image

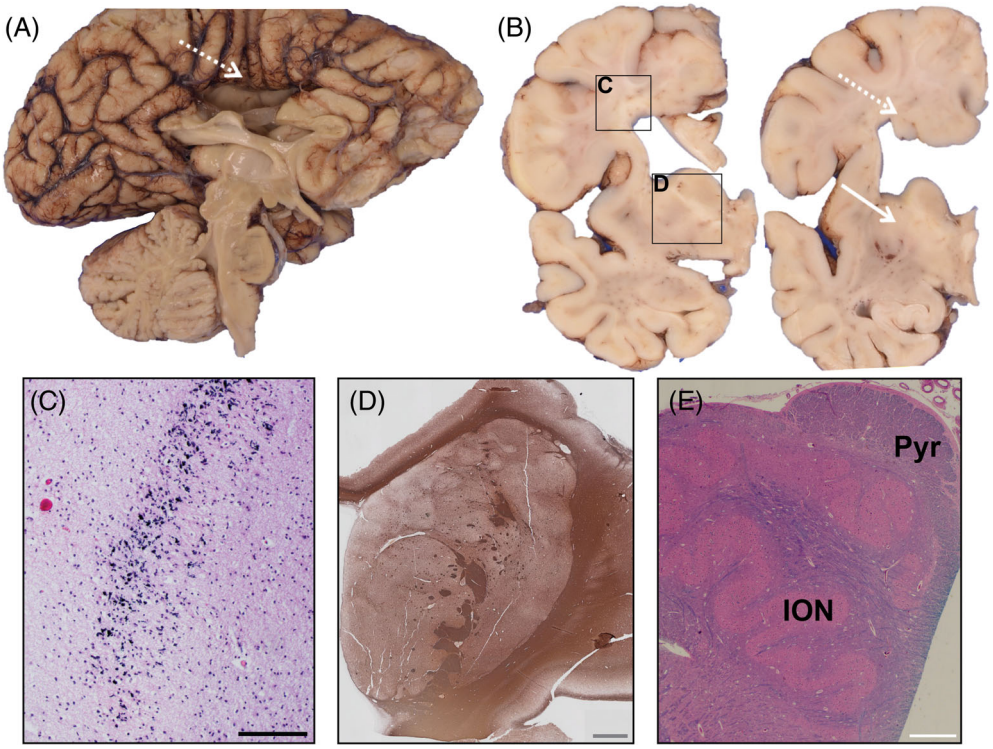


**FIGURE 2** Gross and histologic findings of the patient's brain. (A) Whole hemisphere showing the absence of the corpus callosum (dashed arrow). (B) Sections highlighting the malformation of the basal ganglia (filled arrow) and absence of the corpus callosum (dashed arrow). (C) Areas of calcification in the white matter on LFB-H&E, which show minimal myelination consistent with age (region shown in B). (D) Low magnification of missing pencil fibers in the putamen on Neurofilament (region shown in B). (E) Low magnification image of the medullary pyramid on LFB. ION-inferior olivary nucleus, Pyr-medullary pyramid. Black scale bar = 200 μm, grey scale bar = 2 mm, and white scale bar = 1 mm

contrasting with diffuse high voltage theta and delta slowing in the left hemisphere, along with multiple left sided regions of very active epileptogenicity. An ophthalmologic examination noted left-beating nystagmus.

Loss of milestones by the patient began at 4 months of age, including the loss of oral feeding by 8.5 months, relative microcephaly with developmental regression, and, soon thereafter, the loss of visual tracking and social smiling. Sleep dysregulation required nightly diazepam to manage sleep-associated seizure exacerbations, and the patient experienced medically refractory epilepsy despite polypharmacy. By 17 months, her progressive dystonia required an intrathecal baclofen pump. Episodes of pain, constipation, respiratory illnesses, and other symptoms prompted increasingly frequent and prolonged hospitalizations. At the time of her death, she continued to have frequent seizures despite initiation of a ketogenic diet and an antiepileptic regimen of levetiracetam, vigabatrin, gabapentin, phenobarbital, scheduled diazepam, and parampanel.

## 2 | FINDINGS

Gross examination of the cerebrum showed agenesis of the corpus callosum with associated abnormal gyration in the medial frontal lobes bilaterally and enlargement of the lateral ventricles (Figure 2A,B). Additionally, the basal ganglia were malformed with medial and inferior displacement of the caudate nucleus (Figure 2B,D). There were subtle abnormalities of right peri-sylvian cortical gyration, consistent with that noted on MRI (Figure 1). Multiple areas of infarcts and calcifications were seen in the white matter (Figure 2C; Box 1). There was malformation of the internal capsule, and the pencil fibers in the putamen were hypoplastic (Figure 2D). Finally, examination of a Luxol fast blue (LFB) stain showed atrophy of the medullary pyramid due to fewer descending white matter tracts (Figure 2E). **What is your diagnosis?**

## 3 | DIAGNOSIS

Complex cerebral malformative pattern with basal ganglia abnormalities, corpus callosum agenesis, and medullary pyramid atrophy consistent with neuronal migration disorder associated with *COL4A1* mutation.

## 4 | DISCUSSION

Germline mutations in the *COL4A1* gene have been linked to early-life vascular CNS lesions including porencephaly, vascular injury, and stroke [1]. The largest pathological series in the literature reports four cases with cerebral microvascular thrombosis, hemorrhagic infarcts, and abnormal angiogenesis [2]. Here, we present a unique case of an infant with a *COL4A1* mutation associated with focal hypoxic–ischemic injury and multiple abnormalities of axonal guidance and neuronal migration.

Genetics was heavily involved from the start of this case because of the abnormalities noted on the infant MRI. A microarray was sent, which was normal, but was

followed when the patient was 4 months old by a Neuronal Migration Disorder Flex Panel (Neurology) Plus from Blueprint Genetics in Finland, covering 68 genes including *COL4A1* and *COL4A2*. The results showed that the patient was heterozygous for *COL4A1* c. 2008G > A, p. (Gly670Arg), which is listed in ClinVar as pathogenic/likely pathogenic based on AMG 2015 criteria for classification of mutations.

Our findings suggest the possibility that, in addition to its known role in angiogenesis, *COL4A1* is also directly involved in neuronal development, and particularly in axonal guidance, in humans. This is supported by existing zebrafish data showing that collagen IV plays a role in axonal guidance by regulating basement membrane integrity [3]. The hypoxic–ischemic lesions and agenesis of the corpus callosum presented here mirror previously described findings [2]; however, we described several additional novel abnormalities of axonal guidance and neuronal migration, including the first pathologic diagnosis of these combined histologic features associated with a *COL4A1* mutation.

## AUTHOR CONTRIBUTIONS

SC made the original diagnosis, coordinated, and analyzed clinical data. KLF examined the pathology and wrote the manuscript. LL assisted with manuscript writing. MMH supervised manscript writing. All authors reviewed and approved the final manuscript.

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## KEYWORDS

Axonal guidance, basement membrane, collagen, COL4A1, epilepsy, neurodevelopment

## CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

## DATA AVAILABILITY STATEMENT

Data will be provided upon request to the corresponding author.

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