

Intracranial and Ocular Abnormalities in a Child with Neurodevelopmental Delay

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Case Report

Keywords: COL4A1, Intracranial calcification, Porencephaly, Cataract, Developmental Delay, TORCH

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Abstract

Background: COL4A1 mutations can mimic TORCH infections and should be considered in the differential of congenital infections, especially when additional neuroanatomical abnormalities exist.

Case presentation: A patient with neurodevelopmental delay and an unremarkable prenatal and birth history presented postnatally with congenital cataracts and neuroanatomical abnormalities including periventricular calcifications, porencephaly, and cerebellar hypoplasia. Although there was initial suspicion for a TORCH infection including cytomegalovirus, further genetic testing revealed a novel COL4A1 mutation, which involves type 4 collagen alpha 1 chain, an important component of vasculature.

Conclusions: This case highlights the unique neuroanatomical and extracranial features of COL4A1 mutation which helps differentiate the condition from other related diseases. This report suggests that COL4A1 should be considered in a child with intracranial and ocular abnormalities, particularly in the absence of a perinatal etiology.

Keywords: COL4A1, Intracranial calcification, Porencephaly, Cataract, Developmental Delay, TORCH.

Background

COL4A1 mutations involve the type 4 collagen alpha 1 chain, which is an integral component of vascular basement membranes, particularly in the brain, eyes and kidneys [1]. The resulting fragility of the vasculature can predispose patients to prenatal and postnatal vascular events including micro- and macro-hemorrhage and ischemic damage resulting in white matter disease, calcifications, and periventricular leukomalacia [2]. Porencephaly, or fluid-filled cavities in the brain, develop as a result of the intrauterine or neonatal hemorrhage [3]. Interestingly, silent microhemorrhages occur most commonly in the basal ganglia, supratentorial white matter, and cerebellum. Cerebellar hypoplasia is a characteristic sign of COL4A1 on neuroimaging [1].

COL4A1 can also affect other organ systems [4]. Ocular abnormalities include congenital cataracts, which is the most commonly described eye phenotype. Patients may also show retinal tortuosity, retinal hemorrhages, anterior chamber abnormalities, bilateral microcornea, and unilateral retinal detachment. Renal manifestations present as hematuria, bilateral cysts, and sometimes occur within the complex HANAC syndrome [5]. Related musculoskeletal conditions include Walker Warburg syndrome, which is defined by ocular abnormalities, neuronal migration disorders, and myopathy.

To date, the neurological sequelae of COL4A1 have been described in a limited number of case studies, making the diagnosis difficult [2]. Here, we present a case of a patient with neurodevelopmental delay who presented with unique neuroimaging findings and extracranial manifestations. This unique case informs an approach to differentiating COL4A1 from other similar presentations.

Case Presentation

A 4-year-old girl presented with profound developmental delay, cortical blindness, and epilepsy. She was born to non-consanguineous parents at 40 weeks and 2 days with an unremarkable prenatal history. She did not require resuscitation or a NICU stay. There was no contributory family history. Postnatally, she was found to have microcephaly, mild jaundice, and congenital cataracts. She was significantly delayed in her gross motor and fine motor skills and was nonverbal. She subsequently developed refractory seizures requiring multiple antiepileptic medications.

On examination, her head circumference was two standard deviations below normal. She had roving nystagmus and was unable to fix and follow. She had hypertonicity of her right upper extremity.

An MRI showed periventricular calcifications, left cerebellar hypoplasia, dilatations of the lateral ventricles with porencephaly and white matter volume loss. See Figure 1 for the specific neuroimaging findings. Significant investigations were conducted including a chromosomal microarray, metabolic testing, genetic testing for Rett syndrome and Aicardi-Goutières syndrome. She was also reviewed by the Infectious Diseases team and a TORCH infection was ruled out. Thus, the patient and her parents were enrolled in a further whole exome sequencing study identifying novel genes. The patient was ultimately found to have a *de novo* COL4A1 mutation.

Discussion

This case describes a patient with neurodevelopmental disorder of unknown cause. The patient had a cerebral palsy-like presentation with right hemiparesis and neurological abnormalities arising early in development. In addition, there was evidence of extracranial comorbidities including congenital cataracts and roving nystagmus.

Consistent with the limited reported cases [2], this patient presentation included significant developmental delay, epilepsy, and neuroanatomical abnormalities that could not be attributed to any perinatal etiology. There is also a consistent theme of ocular involvement in previous reports, including visual deficits, cortical blindness, and cataracts. Neuroanatomically, findings of intracranial calcifications were common. This case, however, adds to the existing literature by highlighting additional features including cerebellar hypoplasia and porencephaly, which may be pathognomonic of COL4A1.

The patient's presentation may reflect many underlying etiologies. The presence of microcephaly and precise location of these calcifications in the periventricular area suggests an early pathological process during which neurogenesis and neuronal migration occur. The differential includes infectious causes such as CMV, Aicardi-Goutières syndrome, or PVL secondary to complications of prematurity or other acquired perinatal causes. Investigations for all these etiologies were negative in the current case.

Although intracranial calcifications are shared by many conditions, the porencephaly and cerebellar hypoplasia observed in this case, are features unique to COL4A1 and not seen in CMV, Aicardi Goutières

Syndrome, and PVL arising from prematurity [2]. Moreover, the reported patient presented with ocular abnormalities, which suggests a more systemic vascular disease. Investigations into renal and musculoskeletal abnormalities were not done but may have added additional information to confirm the diagnosis.

Conclusions

COL4A1 can mimic multiple conditions including TORCH infections and ACS. However, unique brain abnormalities can be used to differentiate COL4A1 from other related diseases. Moreover, the presence of extracranial manifestations of disease including ocular abnormalities, nephropathy, and muscle cramps should prompt investigation into systemic involvement of COL4A1 mutation. These clinical features can help clinicians identify when to investigate for COL4A1 in a child with neurodevelopmental delay.

Abbreviations

COL4A1 - Type IV collagen

HANAC - Hereditary angiopathy with nephropathy, aneurysm, and muscle cramps

TORCH - Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, parvovirus B19

CMV – Cytomegalovirus

PVL – Periventricular leukomalacia

Declarations

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Availability of data and materials

All data and material supporting our findings are contained within the manuscript.

Authors' contributions

MR and ES participated the conceptualization of the case report. MR wrote the manuscript. JH helped with manuscript preparation. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written consent was obtained from the mother of the patient for publication of this case report and any accompanying images and details. There is no identifying patient information.

Competing interests

The authors declare no conflicts of interest with respect to the research, authorship, funding, and/or publication of this article.

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Figures

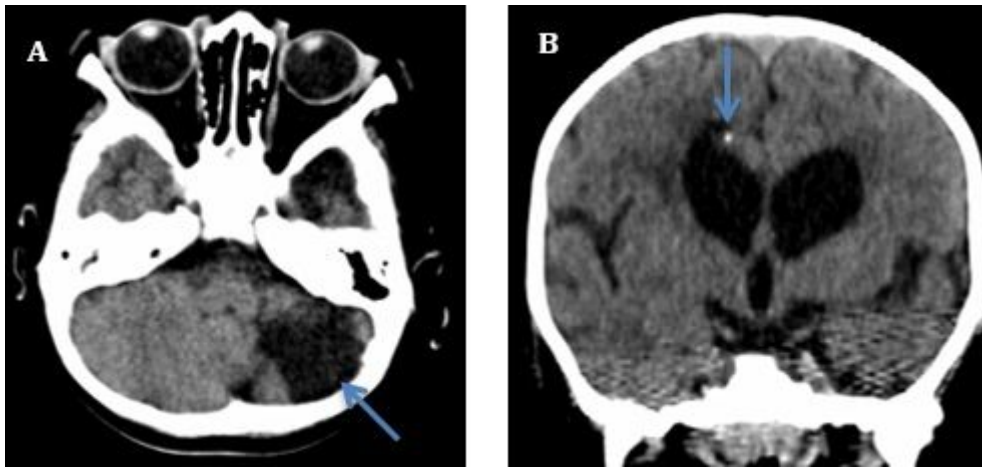


Figure 1

Cerebral tomography scan (A) axial view showing left cerebellar hemisphere hypoplasia (B) and coronal view showing small right porencephalic cyst and adjacent periventricular calcification.

Supplementary Files

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- [supplement1.pdf](#)