Case report

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# Congenital brain malformations associated with *COL4A1* gene mutations: A case series

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## ABSTRACT

Mutations in the *COL4A1* gene, which encodes one of the chains of type IV collagen, affect the basement membrane of various organs, including the brain, eyes, kidneys, and skeletal muscle. These abnormalities can manifest as early as fetal life with a highly variable clinical spectrum, particularly in the central nervous system, where conditions such as intracerebral hemorrhages, porencephaly, hydranencephaly, schizencephaly, hydrocephalus, and periventricular leukomalacia are observed. Extracerebral manifestations include congenital cataracts, intraocular hypertension, hematuria, and arrhythmias. The disease is inherited in an autosomal dominant manner, with complete penetrance.

This article describes three clinical cases with prenatal presentation and pathogenic mutations in *COL4A1*, highlighting their clinical and imaging features, to contribute to timely diagnosis in patients with central nervous system malformations and improve clinical suspicion within the medical field.

***Keywords:*** COL4A1 *gene; collagen disorders; porencephaly; prenatal injuries; hemorrhages.*

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## INTRODUCTION

Type IV collagen is the main component of the basement membrane. It consists of six genetically distinct α-chains. The *COL4A1* and *COL4A2* genes, located on chromosome 13, are expressed in all tissues and encode the α1 and α2 chains, which assemble to form the α1α1α2 heterotrimer.[1] This non-fibrillar collagen is a fundamental component of the basement membranes of multiple organs, including the vascular endothelium.[2] Mutations in *COL4A1* are associated with a systemic disorder of variable presentation, characterized by a broad spectrum of cerebrovascular lesions.[2,3] The condition affects blood vessels in the brain, eyes, kidneys, and skeletal muscle, and may manifest as early as fetal life. Severity ranges from small-vessel disease to fatal intraparenchymal hemorrhages. Among the described cerebral abnormalities are intracerebral hemorrhages, ischemia, porencephaly, hydranencephaly, schizencephaly, cortical malformations, intracranial calcifications, basal ganglia abnormalities, aneurysms, cerebellar involvement, hydrocephalus, polymicrogyria, and periventricular leukomalacia.[1,2] The neurological phenotype includes infantile hemiparesis, spastic tetraparesis, epilepsy, and psychomotor retardation of varying severity, sometimes associated with microcephaly or macrocephaly.[2] Focal seizures, epileptic spasms, and generalized tonic-clonic seizures have been reported.[4] Extracranial manifestations are observed with or without cerebrovascular events.[5] Ocular manifestations include congenital cataracts, optic nerve excavation, intraocular hypertension, anterior segment dysgenesis, and tortuosity of the retinal arterioles. Renal manifestations may include hematuria, renal failure, or renal cysts.[5] Supraventricular arrhythmias, Raynaud's phenomenon, hepatic cysts, muscle cramps with elevated creatine kinase (CK), and migraine have also been reported. *COL4A1*-related disorders are inherited in an autosomal dominant manner, with marked inter- and intrafamilial variable expressivity and complete penetrance.[2,6] Approximately 27% of cases are *de novo* mutations.[6] It has been linked to small-vessel disease in adults, with a high incidence of hemorrhagic strokes.[5] This study aims to describe three clinical cases presenting prenatally with pathogenic mutations in *COL4A1*, highlighting their clinical and imaging features, to provide information in a field that remains uncertain and help to strengthen clinical suspicion in patients with central nervous system malformations during the perinatal period and facilitate timely diagnosis.

## CLINICAL CASE 1

A boy with a prenatal ultrasound diagnosis of germinal matrix hematoma, pseudoporencephaly, and mild ventriculomegaly. He was born at 37.5 weeks due to intrauterine growth restriction. Within the first 24 hours, he presented with seizures, confirmed by polysomnography. A brain magnetic resonance imaging (MRI) scan was performed, revealing pseudoporencephalic cavities, ventricular dilation, reduced cerebellar hemispheres, periventricular calcifications, a cavitary sequelae image, and decreased occipital periventricular white matter. Brain magnetic resonance angiography was normal.

The infant was diagnosed with bilateral congenital cataracts and a small ventricular septal defect (VSD) that resolved spontaneously by one month of age.

At 3 months of age, the child was diagnosed with a collagen disorder caused by a pathogenic variant in the *COL4A1* gene (c.2009G>A; p.Gly670Glu). Parental testing was negative, so the mutation was considered *de novo*.

He presented with growth abnormalities, short stature, low birth weight, microcephaly, microphthalmia, global neurodevelopmental delay, language delay, and hypotonia. At age 3, he began experiencing focal seizures with autonomic symptoms. From a nephrological perspective, he had microscopic hematuria without proteinuria and a normal renal ultrasound.

Currently, at 5 years of age, the patient has no arrhythmias or muscular symptoms, and imaging studies show stable findings with no new bleeding (*Figure 1*).

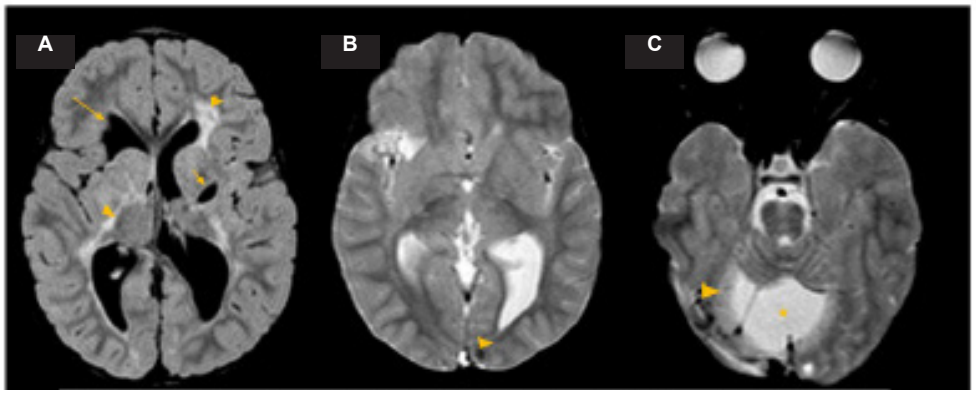
## CLINICAL CASE 2

A boy with a prenatal diagnosis of cerebral cystic lesions. He was born preterm at 36 weeks, with a birth weight appropriate for his gestational age. During his first week of life, he underwent a brain MRI, which revealed polymicrogyria, a residual subpial cystic lesion of hemorrhagic origin, and hemorrhagic lesions.

Subacute intraparenchymal lesions associated with ventricular hemorrhage. No evidence of vascular abnormalities.

By the age of one, he developed microcephaly, global developmental delay, and axial hypotonia. He experienced several episodes of febrile seizures in the context of viral infections.

**Figure 1. Clinical case 1**




***A:*** *Axial section in FLAIR-weighted sequence showing periventricular white matter lesions and involvement of the posterior limb of the internal capsule, predominantly on the right side (arrowhead), a left lenticulo-striate porencephalic cavity (short arrow), and scalloping of the ventricular wall of the anterior horn of the lateral ventricle (long arrow).*
***B:*** *Axial slice in the GRE (gradient-echo) sequence, showing residual hemosiderin in the left occipital cortical-subcortical region (arrowhead).*
***C****: Axial GRE scan at the infratentorial level showing right occipital porencephalic cavities (star) and remnants of chronic hemorrhage (hemosiderin) (arrowhead).*

Ophthalmologically, he exhibited normal fixation and eye tracking. Congenital cataracts and vascular abnormalities were ruled out (normal fundus).

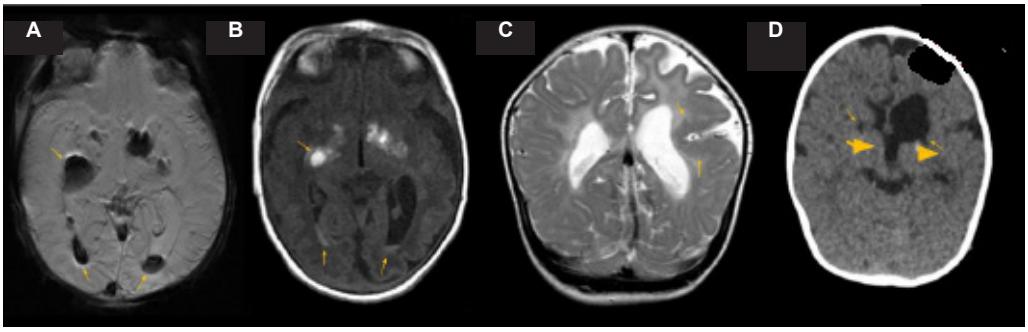
The exome results showed a pathogenic variant affecting the *COL4A1* collagen gene (c.4738G>A; p.Gly1580Ser).

Currently, at 2 years of age, the patient shows no renal, cardiovascular, or muscular symptoms. Imaging studies are stable, with no new bleeding (*Figure 2*).

## CLINICAL CASE 3

A child with a prenatal diagnosis of ventriculomegaly. He was born at term 38 weeks with intrauterine growth restriction. The infant developed microcephaly, neurodevelopmental delay, and poor eye contact. At 3 months of age, he began having seizures with a hypsarrhythmia pattern on the electroencephalogram (EEG), leading to a diagnosis of West syndrome. A brain MRI was performed, which showed enlargement of the lateral ventricles, cystic lesions in the

**Figure 2. Clinical case 2**




***A and B:*** *Non-contrast brain MRI, axial slices in magnetic susceptibility (SWAN) and T1 sequences, respectively, showing bilateral lenticulostriate hemorrhages and intraventricular blood (arrows).*
***C:*** *Follow-up non-contrast brain MRI, coronal T2-weighted sequence; thickening of the left insular cortex is observed, with "nodularity" at the gray-white matter junction consistent with polymicrogyria (PMG). D: Non-contrast brain CT, axial section of the basal ganglia; small sequelae calcifications are identified in the areas of previous hemorrhage (arrowheads) and retractile dilatation of the anterior horn of the left lateral ventricle with adjacent hypodense sequelae (short arrows).*

juxtaventricular white matter, and punctate lesions that could correspond to hemosiderin deposits.

At 8 months of age, a heterozygous pathogenic variant in *COL4A1* (c.2008G>A; p.Gly670Arg) was identified in the exome, confirming COL4A1 collagen disease.

Ophthalmologically, the patient presents with hypotropia, nystagmus, vascular abnormalities characterized by narrowing of the retinal veins and arteries, and abnormalities of the retinal pigment epithelium. The patient also has abnormal visual evoked potentials.

Currently, at 20 months of age, he shows no signs of kidney, cardiovascular, or muscle problems. Imaging studies show stable findings with residual porencephalic lesions and periventricular leukomalacia, with no new hemorrhages (*Figure 3*).

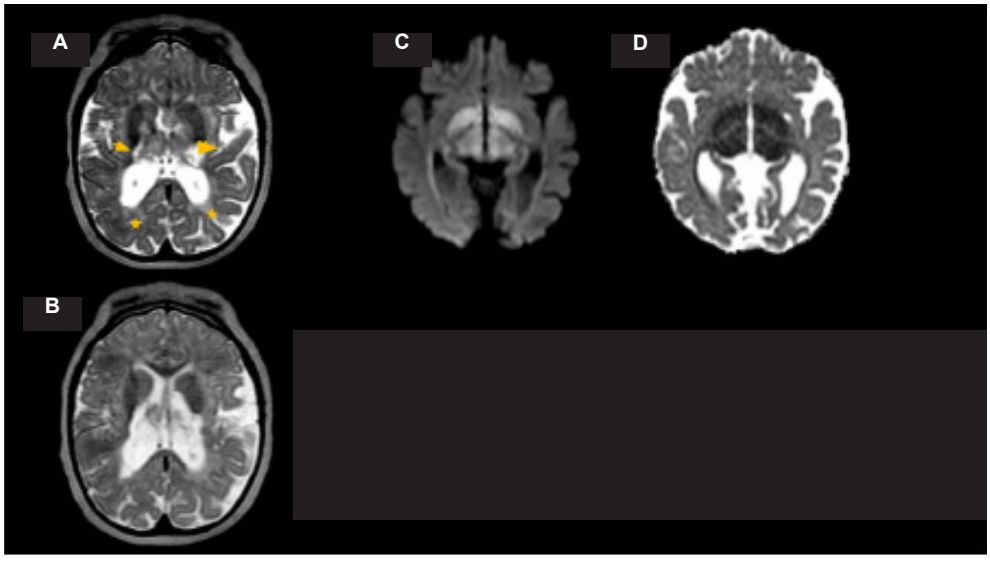
## DISCUSSION

The three cases presented here represent the first local reports of pediatric patients with pathogenic variants in *COL4A1* confirmed by molecular testing in Argentina. Their detection during the prenatal period reinforces the notion that COL4A1-related disorders should be included in the differential diagnosis of congenital brain lesions, particularly in the presence of intracerebral hemorrhage, porencephaly, schizencephaly, hydranencephaly, and hydrocephalus.

Consistent with reports in the literature, all three patients exhibited early neurological involvement, including microcephaly, global developmental delay, and epilepsy. Patient 3 presented with West syndrome, a phenotype recently associated with mutations in *COL4A1,*[3] which broadens the epileptic spectrum to be considered in this disease. The presence of autonomic focal seizures in patient 1 and epileptic status observed in patient 2 are consistent with previous descriptions of epilepsies with early onset and difficult-to-control course *(Table 1*).[1,2,4,5]

Structural abnormalities on neuroimaging were heterogeneous and included intracerebral hemorrhages, porencephaly, polymicrogyria, leukoencephalomalacia, cerebellar hypoplasia, and basal ganglia involvement—findings consistent with those reported by Meuwissen *et al*.[2] and Gasparini *et al*.[1] None of the patients had intracranial

**Figure 3. Clinical case 3**




***A*** *and* ***B****: T2-weighted axial section at the level of the basal ganglia; Periventricular porencephalic cavities are observed; note the left thalamus (yellow arrowhead), hyperintensity in the knee and posterior limb of the right internal capsule (short arrow), as well as mild dilation of the posterior horns of the lateral ventricles and increased signal intensity in the periventricular white matter (stars).* ***B*** *and* ***C****: These correspond to DWI (diffusion-weighted imaging) sequences and an ADC (apparent diffusion coefficient) map, respectively; they show diffusion restriction at the level of the basal ganglia, the dorsal column, and the periventricular white matter at the level of optic radiation.*

**Table 1. Clinical comparison of the three cases with reports in the literature**

| Characteristics | Patient 1 | Patient 2 | Patient 3 | References[1,2,4,5] |
|---|---|---|---|---|
| Time of diagnosis | Prenatal | Prenatal | Prenatal | Prenatal or early childhood |
| Prenatal images | Intracerebral hemorrhage, pseudoporencephaly, ventriculomegaly | Cystic lesions | Ventriculomegaly | lintracerebral hemorrhage, hydrocephalus, ventriculomegaly |
| Epilepsy | Yes, focal autonomic | Yes, tonic.clonic generalized | Yes, West syndrome | Frequent (focal, tonic -clonic, spasms) |
| Developmental delay | Yes | Yes | Yes | Frequent, of varying severity |
| Microcephaly | Yes | Yes | Yes | Common, variable |
| Eye abnormalities | Bilateral congenital cataracts, microphtalmia | Esotropia | Hypotonia, nystagmus, vascular tortuosity | Cataracts, anterior segment dysgenesis, vascular tortuosity |
| Renal | Microscopic hematuria | No | No | Hematuria, renal insufficiency, cysts |
| Cardiac | Mild VSD with spontaneous resolution | Normal | Normal | Arrhythmias, hypertension |
| Muscular | No | No | No | Elevated CPK, muscle cramps |

*VSD: ventricular septal defect; CPK: creatine kinase.*

vascular malformations, which highlights phenotypic variability and supports the hypothesis of an underlying cerebral microangiopathy (*Table 2*).[5]

Regarding extracranial manifestations, the three patients exhibited varying degrees of involvement. Patient 1 presented with microphthalmia, congenital cataracts, and microscopic hematuria, while patient 3 developed ophthalmological abnormalities without renal or cardiovascular involvement at this time. These findings reaffirm the multisystemic nature of the disease (*Table 1*).

In all three cases, the variants were classified as pathogenic, and at least in patient 1, a mutation was confirmed *de novo*. Although the disease is inherited in an autosomal dominant pattern with nearly complete penetrance, its clinical manifestations vary in age of onset and symptom severity.[6] Given the clinical variability and nonspecific imaging findings, a whole-exome sequencing test was ordered in all three cases to guide the diagnosis. Genetic testing allows for confirmation of the diagnosis, determination of appropriate follow-up, and assessment of the prognosis. Furthermore, it helps determine the risk of recurrence and guide family genetic counseling, since these are de novo mutations and the vast majority of cases do not recur within the same family.

These cases illustrate the clinical and radiological heterogeneity of disorders associated with *COL4A1*, highlighting the importance of prenatal suspicion and molecular testing in patients with congenital brain lesions. It is important to perform a differential diagnosis in patients with suspected coagulopathies, perinatal infections such as cytomegalovirus (CMV) and toxoplasmosis, and genetic syndromes. Because of their variable clinical presentation, this group of genetic diseases does not always have a clear clinical suspicion, which is why tests such as whole-exome sequencing—which are broad and less targeted—are often ordered to confirm the diagnosis. Given the multisystemic nature of the disease and the risk of neurological, ophthalmological, renal, and cardiovascular complications, multidisciplinary long-term follow-up is recommended.[1,7,8]

Identifying and reporting new cases in Latin America is essential for expanding our understanding of the phenotype in our population,

**Table 2. Comparison of brain MRI findings in the three cases with those reported in the literature**

| References[1,2,8] | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Porencephaly | Multiple periventricular cysts | Porencephaly | Porencephaly |
| Polymicrogyria | No | Polymicrogyria | No |
| Schizencephaly | No | No | No |
| Hydranencephaly | No | No | No |
| Cerebellar anomaly | Cerebellar hypoplasia | No | No |
| White matter anomaly | Leukoaraiosis, diffuse increase in the intensity of the periventricular white matter | Diffuse enlargement of the intensity of the white matter periventricular and subcortical | Diffuse increase in the intensity of the periventricular white matter |
| Basal ganglia anomaly | No | No | Basal ganglia and brainstem cytotoxic involvement |
| Hydrocephalus | Mild hydrocephalus | No | Mild hydrocephalus |
| Aneurysms | No | No | No |
| Intracranial calcifications | Periventricular calcifications | No | No |
| Hemorraghes | Remnants of chronic hemorrhages | Intraparenchymal and ventricular hemorrhages | Hemosiderin deposits |
| Ischemia | No | No | No |
| Other | Reduced corpus callosum's thickness | Reduced corpus callosum's thickness | No |

establishing regional monitoring protocols, and contributing to the development of targeted therapeutic strategies. ■

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