https://doi.org/10.15446/cr.v10n2.106619

CLINICAL MANIFESTATIONS OF *COL4A1* AND *FGB* MUTATIONS: CASE REPORT

Keywords: *Collagen Diseases*; Fibrinogen; Mutation; Neurodevelopmental Disorders.
Palabras clave: Enfermedades del colágeno; Fibrinógeno; Mutación; Trastornos del neurodesarrollo.

Gerardo Restrepo-Ramirez
Université de Sherbrooke - Faculty of Education - Department of Social and Academic Adaptation Studies - Sherbrooke - Canada

María Juliana Lenis-Patiño
Instituto para Niños Ciegos y Sordos del Valle del Cauca - General Medicine Service - Cali - Colombia

Paola Andrea Acero-Portilla
Universidad CES - Faculty of Medicine - Department of Pediatrics - Medellín - Colombia

María José Hernández-Woodbine
Yale University - Norwalk Hospital - Internal Medicine Residency - California - United States

Corresponding author
Gerardo Restrepo-Ramírez. Département d'études sur l'adaptation scolaire et sociale, Université de Sherbrooke. Sherbrooke. Canada.
E-mail: gerardo.restrepo@usherbrooke.ca

Received: 17/04/2023 **Accepted:** 15/06/2023

ABSTRACT

Introduction: The *COL4A1* gene encodes the alpha-1 chain of type IV collagen, a structural component of basement membranes. In turn, fibrinogen is a large complex glycoprotein consisting of three pairs of polypeptide chains that plays an important role in hemostasis. All of these components are part of membranes in many tissues, including those found in the eyes, kidneys, brain, among other organs. A mutation in these components may result in patients presenting with a variety of clinical manifestations.
Case presentation: An 11-year-old female was referred to the genetics service of a quaternary care institution in Cali (Colombia) due to progressive neurological, renal, and ophthalmologic manifestations. A comprehensive exome sequencing study was performed, revealing two variants: one in the *COL4A1* gene (c.2317G>A) reported as pathogenic and another in the *FGB* gene (c.413C>G) reported as probably pathogenic as per the recommendations of the American College of Medical Genetics and Genomics.
Conclusion: The clinical manifestations of *COL4A1* and *FGB* mutations are varied, and this can delay diagnosis. While there is no specific treatment for the disorders caused by these mutations, preventing complications and treating symptoms can positively impact the quality of life of patients. Therefore, scientific dissemination on this subject is essential.

RESUMEN

Introducción. El gen *COL4A1* codifica la cadena alfa-1 del colágeno tipo IV, un componente estructural de las membranas basales. Por otro lado, el fibrinógeno es una glicoproteína compleja grande formada por tres pares de cadenas polipeptídicas que juega un papel importante en la hemostasia. Cada uno de estos componentes hacen parte de las membranas de muchos tejidos, incluidos los que se encuentran en ojos, riñones, cerebro, entre otros órganos. Una mutación en estos componentes puede llevar a que los pacientes presenten diversas manifestaciones clínicas.
Presentación del caso. Niña de 11 años que fue remitida al servicio de genética de una institución de cuarto nivel de atención de Cali (Colombia) por presentar manifestaciones neurológicas, renales y oftalmológicas progresivas. Se realizó estudio de secuenciación de exoma individual completo que evidenció dos variantes: una en el gen *COL4A1* (c.2317G>A) reportada como patogénica y otra en el gen *FGB* (c.413C>G) reportada como probablemente patogénica según las recomendaciones del American College of Medical Genetics and Genomics.
Conclusiones. Las manifestaciones clínicas de las mutaciones en los genes *COL4A1* y *FGB* son muy diversas, lo cual puede retrasar el diagnóstico. Si bien no existe un tratamiento puntual para los trastornos causados por estas mutaciones, la prevención de complicaciones y el manejo de los síntomas puede impactar positivamente la calidad de vida de los pacientes, por lo que la divulgación científica respecto a este tema es de gran importancia.

INTRODUCTION

The *COL4A1* gene encodes the alpha-1 chain of type IV collagen, which is the main component of basement membranes. Mutations in this gene have rare and clinically diverse manifestations, with onset occurring at different ages ranging from the prenatal stage to late adulthood, thus resulting in an underestimated prevalence.

Primary disorders related to mutations in the *COL4A1* gene include alterations of the renal glomeruli, vascular endothelium, and ocular structures. Clinically speaking, neurological manifestations are the most common and their spectrum varies from cerebrovascular disease, which may present as small vessel disease, to fatal intraparenchymal hemorrhage (2-4). Other clinical manifestations are developmental delay, seizures, infantile hemiparesis, intellectual disability, migraine, and dementia (5).

Performing genetic testing to detect mutations in the *COL4A1* gene is controversial due to its multisystemic nature. At present, no specific therapeutic measure has proven to be effective for the management of this genetic disorder, so interventions and treatments are aimed at alleviating clinical manifestations and preventing secondary complications (2).

On the other hand, fibrinogen is a hexameric plasmatic glycoprotein composed of pairs of three chains (Aα, Bβ, and γ) that play a key role in hemostasis. The conversion of fibrinogen into insoluble polymeric fibrin provides structural stability, strength, and adhesive surfaces for the growth of blood clots. Diseases affecting fibrinogen can be inherited or acquired. Congenital fibrinogen deficiencies are rare bleeding disorders characterized by extensive genetic heterogeneity in the *FGA*, *FGB*, and *FGG* genes, which encode the Aα, Bβ, and γ chains, respectively. Depending on the type and location of mutations, congenital fibrinogen defects can result in multiple clinical manifestations, going from asymptomatic conditions to life-threatening hemorrhage or even thromboembolic events (6).

Patients with a variant of the *FGB* gene, such as dysfibrinogenemia, may present different symptomatology. According to Haverkate & Samama (7), there are 250 reported cases of patients with dysfibrinogenemia, of which 53% were asymptomatic, 26% had bleeding events, and 21% had thrombosis. Fibrinogen disorders with severe manifestations are rare; however, there are reports of patients with cerebral hemorrhage, umbilical hemorrhage, musculoskeletal hemorrhage, and scarring disorders (8).

CASE PRESENTATION

An 11-year-old female from Cali, Colombia, was referred in 2019 (when she was 9 years old) to the genetics service of a quaternary care institution in Cali after being diagnosed with multiple conditions (glaucoma, congenital cataract, microcornea, focal epilepsy, right hemiparesis, and neurogenic bladder). She also presented with recurrent episodes

of urinary tract infection and difficulties in reaching the developmental milestones expected for her age.

The patient was the product of a second 38-week pregnancy born to a 22-year-old woman, and during her gestation, the mother attended a reasonable number of prenatal check-ups. Her birth weight was 3 765g and her length was 48cm, and since she had an adequate neonatal adaptation, she was discharged promptly. Relevant history included one episode of threatened preterm labor at 25 weeks and a screening immunoglobulin blood test performed 23 days after birth for rubella, which reported positive IgG and negative IgM antibodies, suggesting past exposure to the virus and inactive infection.

From the age of 4, the patient was taken to several medical consultations with various specialists, receiving multiple diagnoses (mentioned above); she also had to be admitted to the hospital on some occasions. Since then, outpatient follow-up by nephrology, ophthalmology, neuropediatrics, gastroenterology, orthopedics, psychiatry, and genetics was implemented. The neuropediatrics service ordered a treatment with levetiracetam (30mg/kg/day orally), as well as physical, occupational, and speech therapy sessions. At the same time, the nephrology service indicated intermittent catheterization and continuous monitoring of renal function.

Due to the multiple and diverse clinical manifestations, in 2019, at the age of 9 years, the patient was referred to the genetics service of a quaternary care institution in Cali, where she underwent whole exome sequencing that showed two genetic variants: one in the *COL4A1* gene (c.2317 G>A), reported in databases as pathogenic, and another in the *FGB* gene (c.413C>G), which was classified as probably pathogenic (Table 1) based on the recommendations of the American College of Medical Genetics and Genomics (9).

Table 1. Whole exome sequencing of the reported patient.

Gene	Genetic variant	Genotype	Clinical significance
COL4A1	NM_001845.6: c 2317G>A NP_001836.3: p. Gly773 Arg	Heterozygous	Pathogenic
FGB	NM_005141.5:c.413C>G NP_005132.2:p.Ser138Cys	Heterozygous	Probably pathogenic

Source: Own elaboration.

In view of these results, the origin of the conditions described was reconsidered, suggesting that the clinical spectrum was secondary to a genetic condition. To determine the presence of family mutations, parents were instructed to undergo molecular testing for the altered genes (*COL4A1* and *FBG*). These tests were performed in 2021, showing that the father's results were negative for the variants of clinical interest, while the variant in the *FGB* gene (c.413C>G) was present in the mother, although no changes were found in the *COL4A1* gene (Table 2); it should be

noted that up to that moment, the mother had not experienced any clinical manifestation caused by the reported variant. Since there was no other known family history related to these mutations, a genetic study was recommended for the siblings (aged 2 and 15 years). However, at the time of writing this case report, the results were not yet available due to administrative processes carried out by their health care provider. Figure 1 shows the family tree with the genetic findings.

Table 2. Molecular study performed on the mother of the reported patient.

Gene	Genetic variant	Genotype	Clinical significance
FGB	*NM_005141.5:c.413C>G NP_005132.2:p.Ser138Cys*	*Heterozygous*	*Probably pathogenic*

Source: Own elaboration.

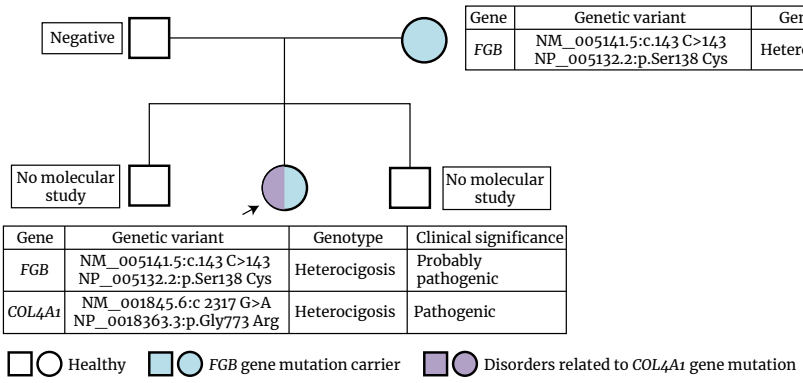

Figure 1. Family tree with genetic findings.

Source: Own elaboration based on the results from the genetic study.

According to neuropediatrics, the patient was independent to perform multiple activities of daily living and received special education due to her sensory-visual, cognitive, and language disorders. However, since the second half of 2021, at the age of 11 years, she presented an increase in her functional limitation, with progressive regression in her language and motor skills (paresthesia in lower limbs and, later, right and left hemiparesis until requiring a walker to move around, with a functional level of III according to the gross motor function classification system - GMFCS).

Due to the deterioration of the patient's condition, the caregivers requested a neuropediatric assessment in November 2021. During the consultation, the patient presented difficulty standing upright and walked with great instability. Physical examination showed head circumference of 55cm (negative for microcephaly), strength in right lower limb of 3/5, strength in right upper limb of 3/5, strength in left lower limb of 4/5, and strength in left upper limb of 5/5 (Daniels muscle testing). There was also evidence of right patellar reflex, decreased left

patellar reflex, and dysarthria. A follow-up magnetic resonance imaging (MRI) scan of the brain requested by the genetics service one month before assessment by the neuropediatrics department showed confluent hyperintensities of the periventricular white matter suggestive of an old hemorrhage, in addition to hypomyelination and arachnoid cysts located in the right temporal lobe and the cisterna magna.

The opinion of the neuropediatric service was that these entities could not be secondary to congenital rubella because the patient did not meet the diagnostic criteria and there was no history of perinatal complications. Therefore, it was considered that the findings were related to deterioration caused by leukoencephalopathy secondary to microangiopathy associated with fibrinogen alteration. As a result, the genetics service referred the patient to the pediatric neurology service and made recommendations for follow-up.

DISCUSSION

The *COL4A1* gene is located on the long arm of chromosome 13 (13q34), consists of 52 exons (1,10-12), and encodes the alpha-1 chain of type IV collagen, a fundamental component of basement membranes as it confers stability (1). The alpha chains of collagen IV (α1 to α6) form 3 heterotrimers (α1α1α2, α3α4α5, and α5α5α6), which in turn form collagen networks and are responsible for membrane strength and integrity (13-15).

On the other hand, fibrinogen is a plasma glycoprotein involved in hemostasis by forming the fibrin clot and mediating platelet aggregation (16). Congenital fibrinogen defects are rare bleeding disorders with a wide genetic heterogeneity in the *FGA*, *FGB* (observed in the present case report), and *FGG* genes (6). Depending on the type and site of occurrence of the mutations, patients may be asymptomatic or experience different bleeding manifestations, ranging from mild to catastrophic (6,16), accounting for 9.3% of cases of rare bleeding disorders and being more frequent in females than in males (6).

Mutations in the *COL4A1* gene are mostly missense mutations involving a glycine residue in the translated regions, causing the synthesis of an abnormal protein and vessel wall fragility (17,18). Disorders related to mutations in the *COL4A1* gene are autosomal dominant and most people diagnosed with these disorders have an affected parent. It is estimated that less than 27% of cases are caused by a de novo pathogenic variant (1), as was the case of the patient reported. This type of disorder occurs more frequently in young adults and children, and there have even been cases reported in newborns (19).

The most frequent manifestations of *COL4A1* gene mutations are neurological, which can present as prenatal and perinatal hemorrhages, congenital aneurysms, and sporadic or recurrent intracerebral hemorrhages that occur spontaneously or

from trauma and the use of anticoagulants (20). Other neurological manifestations described are porencephaly, infantile hemiparesis, developmental delay, seizures, intellectual disability, and cognitive impairment (21).

It should be noted that, recently, mutations in the *COL4A1* gene have been recognized as a monogenic cause of cerebral small vessel disease, generating greater susceptibility to ischemic stroke or cerebral microhemorrhage (22,23), as in the patient described in this case.

Furthermore, it has been demonstrated that collagen plays an important role in the etiology of cerebrovascular disease since defects in the basement membrane weaken the blood vessels, and the anatomy of the microvasculature (made up of small, deep, penetrating arteries) becomes more vulnerable (22,23). Regarding ophthalmologic involvement, there are reports of patients with cataract, juvenile-onset glaucoma, retinal arteriolar tortuosity, and ocular anterior segment dysgenesis (24). Nephropathy is another reported manifestation and its presentation may include macroscopic and microscopic hematuria, renal cysts, kidney failure, and kidney agenesis (25-27).

The wide spectrum of clinical manifestations due to *COL4A1* and *FGB* gene mutations, which can generate a high burden of morbidity and mortality, explains the clinical deterioration of our patient. In this sense, the present case is considered relevant since the patient presented several of the symptoms described in the literature, and it also shows the importance of working together with other specialties given the complexity of the clinical manifestations of these mutations.

CONCLUSIONS

The clinical manifestations associated with mutations in the *COL4A1* (pathogenic) and *FGB* (probably pathogenic) genes are quite varied, which may delay diagnosis. Although there is no treatment for the disorders caused by these mutations, the prevention of complications and the management of symptoms can positively impact the quality of life of patients, making the scientific dissemination of these cases highly relevant.

ETHICAL CONSIDERATIONS

The patient's family signed the informed consent form authorizing the anonymous dissemination of the case and its results.

CONFLICTS OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

To the Instituto para Niños Ciegos y Sordos del Valle del Cauca for making the work of the researchers easier.

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