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SCIENTIFIC LETTER

Kidney manifestations of *COL4A1* mutations: a report of three cases

Manifestaciones renales de mutaciones *COL4A1*: serie de tres casos

To the Editor:

The most common hereditary cause of microscopic haematuria is the presence of pathogenic variants in the *COL4A3*, *COL4A4*, or *COL4A5* genes encoding type IV collagen.

The autosomal dominant inheritance of pathogenic *COL4A1* variants has been recognised as a monogenic cause of ultrastructural basement membrane defects with widespread manifestations, including renal involvement.[1,2]

We report 3 cases of pathogenic *COL4A1* variants in paediatric patients:

Clinical case 1: Girl aged 3 years with a history of intrauterine growth restriction with diagnoses of microcephaly, symptomatic epilepsy and cerebral palsy. Magnetic resonance imaging (MRI) revealed periventricular calcifications and anterior segment dysgenesis, compatible with Axenfeld-Rieger syndrome. There was persistent microhaematuria in the urine sediment, with no other markers of renal failure, and an incidental finding of left grade I/IV hydronephrosis in the abdominal ultrasound scan. The patient had no history of urinary tract infection (UTI). Whole-exome sequencing (WES) identified a de novo heterozygous missense gene variant in exon 11 of the *COL4A1* gene, c.634 G > C; p.(Gly212Arg). This variant had not been described in the general population or in affected patients, but due to its de novo nature and its impact on an amino acid crucial to the structural integrity of collagen, we considered it to be pathogenic.

Clinical case 2: Boy aged 12 years with previous diagnosis of occipital encephalocoele (treated with a ventriculoperitoneal shunt), Arnold-Chiari malformation type 1, mild psychomotor retardation, microcornea and congenital cataract with bilateral optic atrophy. At age 10 years, he presented with macroscopic haematuria with persistent microhaematuria in absence of proteinuria with normal findings in the abdominal ultrasound. Whole-exome sequencing identified a de novo heterozygous variant in *COL4A1*, c.3244 G > A; p.(G1082R), considered pathogenic.

Clinical case 3: Girl with a history of intrauterine growth restriction, microcephaly, encephalopathy, severe psychomotor retardation and marked absence of white matter myelination on MRI. The ophthalmological findings included nystagmus, strabismus, and microphthalmia. At age 10 years, she developed chronic kidney disease, arterial hypertension, proteinuria and hyperuricaemia, which were treated conservatively. There was no associated microhaematuria at any point in the course of disease. The relevant family history included parental consanguinity and psychomotor retardation in a sister. Whole-exome sequencing identified a homozygous *COL4A1* variant, c.1366 G > A; p.(Glu456Lys), which is considered pathogenic. The patient died of respiratory failure at age 15.

Based on the clinical presentation of the 3 patients, renal manifestations should be considered a part of the broader clinical spectrum associated with pathogenic *COL4A1* variants.[1,3] While these variants were initially recognised as causing small vessel disease and other neurological disorders, it is now evident that they can also affect the eyes and the kidneys.[1,4]

From a nephrourological perspective, pathogenic *COL4A1* variants are primarily associated with microhaematuria. *COL4A1* encodes the proα1(IV) chain of type IV collagen, a key component of basement membranes in various tissues including vascular endothelia.[2,4] Recent studies have identified pathogenic heterozygous *COL4A1* variants as a potential new autosomal dominant cause of congenital anomalies of the kidney and urinary tract (CAKUT), primarily due to non-glycine substitutions, with vesicoureteral reflux as the predominant manifestation.[5]

Persistent microhaematuria, which is the most common renal manifestation described in the literature, occurred in 2 of our 3 patients. Hydronephrosis, a component of CAKUT, was identified in only 1 patient, although a voiding cystourethrogram was not performed due to the absence of UTI and the low grade of hydronephrosis. Other clinical manifestations of renal kidney involvement, such as renal cysts, have been described frequently,[1,4] but were not present in any of our patients.

In this case series, the observed neurologic and ophthalmological manifestations were consistent with the previous literature. The ophthalmological manifestations include congenital cataracts, retinal arterial tortuosity and Axenfeld-Rieger-type anterior chamber abnormalities.[2–4]

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The neurologic manifestations include antenatal or perinatal cerebral haemorrhage, encephaloclastic lesions secondary to haemorrhagic venous infarction, porencephaly, and epilepsy.[3,4,6]

We report 3 cases of pathogenic *COL4A1* variants associated with renal manifestations. Based on these findings, we recommend screening for renal involvement, especially glomerular disease and CAKUT, in patients with *COL4A1* changes. Additionally, we suggest considering this condition in patients with persistent microhaematuria.

References

1. Shah S, Ellard S, Kneen R, Lim M, Osborne N, Rankin J, et al. Childhood presentation of COL4A1 mutations. Dev Med Child Neurol. 2012;54(6):569–74, http://dx.doi.org/10.1111/j.1469-8749.2011.04198.x. Epub 2012 Jan 16. PMID: 22574627.
2. Gale DP, Oygar DD, Lin F, Oygar PD, Khan N, Connor TM, et al. A novel COL4A1 frameshift mutation in familial kidney disease: the importance of the C-terminal NC1 domain of type IV collagen. Nephrol Dial Transplant. 2016;31(11):1908–14, http://dx.doi.org/10.1093/ndt/gfw051. Epub 2016 Apr 8. PMID: 27190376; PMCID: PMC5091614.
3. Meuwissen MEC, Halley DJ, Smit LS, Lequin MH, Cobben JM, De Coo R, et al. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. Genet Med. 2015;17(11):843–53, http://dx.doi.org/10.1038/gim.2014.210. Epub 2015 Feb 26. PMID: 25719457.
4. Plaisier E, Gribouval O, Alamowitch S, Mougenot B, Prost C, Verpont MC, et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med. 2007;357(26):2687–95, http://dx.doi.org/10.1056/NEJMoa071906. PMID: 18160688.
5. Kitzler TM, Schneider R, Kohl S, Kolvenbach CM, Connaughton DM, Dai R, et al. COL4A1 mutations as a potential novel cause of autosomal dominant CAKUT in humans. Hum Genet. 2019;138(10):1105–15, http://dx.doi.org/10.1007/s00439-019-02042-4. Epub 2019 Jun 22. PMID: 31230195; PMCID: PMC6745245.
6. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. Neurology. 2018;91(22):e2078–88, http://dx.doi.org/10.1212/WNL.0000000000006567. Epub 2018 Nov 9. Erratum in: Neurology. 2020 Feb 18;94(7):332. doi: 10.1212/WNL.0000000000008787. PMID: 30413629; PMCID: PMC6282239.

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