

sible genetic etiology. The unit found a homozygous mutation in the FAN1 gene associated with karyomegalic interstitial nephritis with an autosomal recessive inheritance pattern. The patient is a carrier of the probably pathogenic variant c.1578-1G>T in homozygosis in the FAN1 gene.

This is one of the rare cases of karyomegalic interstitial nephritis confirmed via genetic study published in the literature. The prevalence of this entity is very low (<1/1,000,000) and there are very few cases described. FAN 1 is considered an effector of the Fanconi pathway, a DNA damage response signaling pathway dedicated to repair DNA interstrand crosslink damage. However, no FAN1 mutations were detected in Fanconi anemia⁶ because Fanconi anemia involves other nucleases in its pathogenesis.⁷ These differences in cellular phenotypes lines may explain the lack of apparent phenotypic similarities between FAN1-negative individuals, compared to those who present karyomegalic interstitial nephritis, and Fanconi individuals who have clinical disease.⁸

We would like to highlight the fact that there is a high percentage of individuals treated with renal replacement therapy, diagnosed with fibrotic nephropathy of unknown cause, in which further studies should be done as well as genetic causes should be considered. Also, to emphasize the importance of renal biopsy as a diagnostic tool, and the importance of giving a name and surname to the renal diseases we treat.

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X-linked hypophosphatemia: long-term outcomes of different treatment strategies

Hipofosfatemia ligada al cromosoma X: resultado a largo plazo con diferentes modalidades de tratamiento

Dear Editor,

X-linked hypophosphatemia (XLH) has an incidence of 1/20,000 newborns.¹ It is caused by loss-of-function muta-

tions of the PHEX gene, resulting in excess circulating fibroblast growth factor 23 (FGF23), with renal loss of phosphate and decreased synthesis of 1,25-dihydroxyvitamin D.² Chronic hypophosphatemia leads to rickets and osteoma-

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Table 1 – PHEX gene mutation.

Case ID	Gen	Position	Variation	Result	Copies
1 ^a	PHEX	ChrX:22.099.105	C > T	p.Gln345*: glutamine substitution by premature termination codon	Hemizygosis (1 copy)
2 ^a					
3 ^a					
4 ^b	PHEX	ChrX:22.247.942	C > T	p.Arg747*: arginine substitution for premature termination codon	Heterozygosis (1 copy)
5 ^b					
6 ^b					
7 ^c	PHEX	ChrX: 22.056.58 9–22.056.590	AG > A	p.Ser411Ilefs*5: substitution of serine for isoleucine and change of reading frame with a consequent premature termination codon	Heterozygosis (1 copy)
8 ^c	PHEX	ChrX: 22.077.58 1–22.077.585	CAGAG > C	p.Arg183Serfs*37: substitution of arginine for serine and change of reading frame with a consequent premature termination codon. Somatic mosaicism affecting 55% of somatic cells	Hemizygosis (1 copy)

^a First family: the initial patient (case 1) was genetically confirmed. He had four siblings, one of them (case 2) and a daughter (case 3) with the same diagnosis.

^b Second family: the mother had a diagnosis of rickets that was confirmed as XLH by genetic study when the disease was suspected in her daughter (initial case 4) and later in the other children (cases 5 and 6).

^c Cases 7 and 8 had *de novo* mutations.

lacia, growth retardation, lower limb malformations, pain and decreased physical function, mobility and quality of life.^{1,3} Conventional replacement therapy (phosphate salts and 1,25-dihydroxyvitamin D⁴ does not correct hypophosphatemia and may induce hypercalciuria, nephrocalcinosis and hyperparathyroidism. Moreover, it is difficult to implement, especially in children, given the gastrointestinal side effects and the need for frequent dosing.^{3–5} Burosumab (a recombinant human monoclonal antibody against FGF23) improves renal tubular phosphate reabsorption (RTP) with increased levels of phosphorus and 1,25-dihydroxyvitamin D.⁶

We conducted an observational, longitudinal, retrospective study at a referral hospital in Bahía Blanca, Argentina, to report the long-term outcome of patients with genetically confirmed XLH rickets from 1997 to 2022. Demographic and clinical data at diagnosis, imaging studies, and initial and subsequent laboratory results were recorded. Healthcare workers conducted check-ups every 3–6 months and a dental examination annually. A jugal mucosa sample was collected from one member of each family for a next-generation sequencing panel of 13 genes with different inheritance patterns. Treatment-related data were also obtained.

Eight patients (four males) with a median age at diagnosis of 1.9 years (range: 0.75–2.75), followed for a median of 7.16 years (range: 2–24), were included. Six patients were members of two families; the other two patients had *de novo* variants that had not been previously described (Table 1). Clinical manifestations and laboratory data at diagnosis are shown in Table 2. Half were growth retarded; disproportionate

short stature, lower limb malformations and abnormal gait were observed in most patients. All had limitations in daily activities (jumping, running, walking), severe radiological abnormalities (cupped metaphysis, widened and irregular epiphyses of long bones), low phosphorus levels, normal calcium and parathormone values, and high alkaline phosphatase levels. Four patients had RTP < 85% and all participants were characterized by maximal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR) < 3.8 mg/dl. FGF23 levels were variable (Table 2).

After diagnosis, all patients received continuous phosphate replacement therapy with 5 daily doses of phosphate salts (average: 40 mg/kg/day) and 0.25 µg/day of 1,25-dihydroxy vitamin D. Adherence was difficult due to gastrointestinal intolerance; improvement of radiological rickets lesions was observed in the first year of treatment, without restoration of phosphorus levels. In the long term, all patients had persistent radiological signs of rickets and residual bone malformations. Four patients maintained short stature. No patient developed hypercalciuria, nephrocalcinosis, hyperparathyroidism or dental abscesses.

Due to persistent rickets, musculoskeletal pain, limitation of daily activities and fractures, two children and two adults were rotated to subcutaneous burosumab after receiving replacement therapy for a median of 6 and 18 years, respectively. Children received 0.8 mg/kg every two weeks; adults, 1 mg/kg every four weeks, with discontinuation of conventional therapy two weeks earlier. After starting burosumab, all patients reported significant improvement in physical activities, with less fatigue and no pain. Height gain was observed in

Table 2 – Clinical and biochemical findings at diagnosis.

Case	Age (years)	Sex	Signs and symptoms	Height		Serum phosphorus	FAL	TmP/TFG	FGF23
				Percentile	Z-score				
1	2	Male	Arching of the lower extremities, abnormal gait, pain	p 1.55	–2.16	3.7	1.712	1.8	7.78
2	1.5	Woman	Abnormal gait, widening of the wrists	p 22.5	0.75	2.3	2.346	1.86	231
3	1	Woman	Arching of the lower limbs	p 50	0	3.6	1.760	3.19	3.106
4	2.75	Woman	Stunting	p 2.31	–2	3.4	1.295	2.9	46
5	2.41	Male	Widening of the wrists	p 1.86	–2.08	2.6	422	2	66
6	0.75	Male	Stunted growth, scaphocephaly	p 0.14	–3	3.5	907	3.15	606
7	1.83	Woman	Arching of the lower extremities, abnormal gait, pain	p 27	–0.61	2.8	566	2.5	No data
8	2	Male	Arching of the lower limbs	p 15.6	–1	2.7	1.897	2.23	11.358

ALP: alkaline phosphatase; FGF23: fibroblast growth factor 23; TmP/GFR: maximal tubular phosphate reabsorption per glomerular filtration rate. Reference values (1–3 years of age): phosphorus = 3.9–6 mg/dl; FAL = 116–294 UI/l; TmP/TFG = 3.8–5 mg/dl; FGF23 = 0–134 pg/ml. Cases 1 to 3 had the same mutation. Cases 4 to 6 had the same mutation. Cases 7 and 8 had *de novo* mutations.

two patients who started burosumab during infancy, reaching a Z-score of –0.2. Normalization of phosphorus and TmP/GFR was verified. Radiological signs of rickets disappeared in all these patients. No serious adverse reactions were observed.

In patients with XLH, phosphate supplementation can stimulate FGF23 levels and renal phosphate excretion, with a vicious cycle that limits its efficacy.³ Conventional therapy is unsuccessful in many cases, and up to two-thirds of children require lower limb surgery.⁷ Burosumab has been shown to be safe and effective, with improvement in TmP/GFR, hypophosphatemia, linear growth and functional capacity, as well as decrease in pain and severity of rickets.^{6,8,9} Four of our patients were rotated to burosumab, with clinical and biochemical improvement and complete resolution of radiological signs of rickets. These results were most notable in children.

We conclude that, in our long-term study with continuous follow-up, the main finding is the marked improvement of biochemical, radiological and especially clinical manifestations in patients who rotated from conventional treatment to burosumab.

Conflict of interest

The authors report no conflicts of interest.

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Fibrillary glomerulonephritis: more frequent than it seems? The diagnostical importance of immunohistochemistry

Glomerulonefritis fibrilar: ¿Más frecuente de lo que parece? La importancia de la inmunohistoquímica en el diagnóstico

Dear Editor,

Fibrillary glomerulonephritis (FGN) is a rare entity defined by the finding of randomly arranged, unbranched fibrils between 15 and 25 nm in diameter in electron microscopy (EM).¹ 5 patterns have been defined in optical microscopy (OM) related to clinical presentation and prognosis.^{2–5} However, the greatest contribution to the diagnosis of this entity has been the discovery of the immunohistochemical marker DNAJB9, a marker with a sensitivity of 98% and a specificity of 99%.^{6,7} Furthermore, the use of the C4d marker, widely used in other kidney diseases,⁸ can contribute to the diagnosis.

We present 5 cases of FGN with epidemiological, diagnostic and associative relevance (Table 1 and Fig. 1). The incidence of FGN is lower than 1%,^{1–4} but the incidence of our sample is higher, with 5 cases among 135 biopsies performed, providing an incidence of 3.7%. This could be justified by the recent discovery of the DNAJB9 marker as a diagnostic tool.

Clinically, it usually begins in the fifth or sixth decade of life, with a predominance in Caucasian women, as occurred in our cases. There is a broad clinical spectrum, with the most common being the association of deterioration in renal function, proteinuria and microhematuria.¹ In our series, 3 of the 5 patients had altered renal function at the onset, all had proteinuria, 4 of them were in the nephrotic range, and 3 had microhematuria.

Its association with the hepatitis C virus, dysproteinemias, autoimmune diseases, diabetes mellitus and malignancy has been described.^{2–4} In our series, 2 patients presented tumour disease (breast adenocarcinoma and hepatocellular carcinoma) and one patient presented ANA⁺, without correlating with autoimmune disease. There is also a case with diagnosed recurrent myelitis, classified as idiopathic, and a case with a family history of unknown glomerulopathy. The literature describes some cases of familial association of FGN, such as

the paper published in 2015 by Ying T et al., in which two Australian families were diagnosed with FGN with an autosomal dominant inheritance pattern.⁹

In the BM, we found 2 cases of isolated mesangial pattern, 2 cases with a combination of mesangial and membranous pattern and one case with diffuse sclerosing pattern. Similar to the literature,^{1–4} the 2 patients with a mesangial pattern presented better outcomes. Two patients had a mixed mesangial and membranous pattern, which, although in isolation, have been correlated with a better prognosis. The association of patterns could explain the worse evolution, especially for case number 4. Finally, the patient with a sclerosing pattern diffuse presented poor evolution.

The recent discovery of DNAJB9 as a diagnostic tool,^{6,7} with a sensitivity of 98% and a specificity >99%, has meant an important advance in histological diagnosis. It may even avoid performing ultrastructural studies in patients with positive DNAJB9. In our series, 4 of the patients were DNAJB9 positive, avoiding the use of EM in one of the cases. For the last case, with DNAJB9, negative Congo red ruled out the possibility of advanced amyloidosis, and the advanced optical microscopy pattern ruled out the possibility of incipient amyloidosis. Finally, electron microscopy confirmed the diagnosis, this being the *gold standard examination*.

Although DNAJB9 is a highly specific tool, it is not routinely performed in all renal biopsies, so there must be a prior histopathological suspicion to request it. The use of markers such as C4d, widely used in other kidney diseases, was key for the differential diagnosis in case 4, previously diagnosed with membranous nephropathy, since upon observing that in addition to the classic pattern of membranous deposits, there was also mesangial deposits, which led to considering other diagnoses, requesting DNAJB9 and EM, and thus confirming the diagnosis.

No optimal therapy for fibrillary glomerulonephritis has been established to date.¹ In addition to conservative medical