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Letter to the Editor

Story of two sisters with kidney disease: Genetics command☆

Historia de dos hermanas con enfermedad renal: la genética manda

Dear Editor,

Advances in technology and cost-efficiency of mass sequencing analyses with next-generation-sequencing (NGS) are allowing clinical laboratories like ours to integrate genetic diagnosis into the routine care of patient, in the interest of the new scenario that personalised and precision medicine is offering, the development of which is facilitating and improving the connection between classical anatomical-clinical findings and genetic characteristics.

Chronic kidney disease (CKD) continues to grow among people over 70 years of age with diabetes and hypertension, with progression being more accentuated in men. However, we still know little about the magnitude of hereditary CKD, which is estimated to be between 30% and 70%, and there are already numerous genes involved in this pathology.[1]

We explain how the diagnosis of a hereditary glomerular disease was achieved after years of progression. We present two cases of Alport syndrome (AS), a systemic disease characterised by renal, otorhinolaryngological (ENT) and ocular involvement, underdiagnosed, and whose true incidence and prevalence will be defined in the coming years, thanks to the involvement of genetic studies.[2]

The cases are two sisters, 39 and 33 years old, of consanguineous parents. At the age of 11, the older sister first presented with nephrotic syndrome, microhaematuria, hypertension (HTN) and renal failure (serum creatinine 1.7 mg/dl). Ultrasound revealed bilateral nephromegaly with loss of cortico-medullary differentiation and slight cortical echogenicity. A renal biopsy by microlumbotomy was performed, which established the diagnosis of membranoproliferative glomerulonephritis type I (MPGNI). Treatment based on steroids and cyclophosphamide for two years did not prevent the progression of kidney failure, and the patient required a kidney transplant at the age of 13.

Microhaematuria was detected in the younger sister at seven years of age. Eight years later, she presented with nephrotic syndrome and the diagnosis of focal segmental glomerulosclerosis (FSGS) was established after a percutaneous renal biopsy. Patient's CKD progressed and at the age of 19 she required haemodialysis and kidney transplantation was performed one year.

Years later, both were diagnosed with bilateral sensorineural hearing loss, and currently need to wear hearing aids. In this context, AS was suspected, and in 2015 a genetic study was performed to the older sister, in which the variant c.345del (p.Pro116Leufs * 37) in exon 6, in the *COL4A3* gene was identified in homozygosis, described as pathogenic for AS. In 2016, this same genetic condition was confirmed in the younger sister.

AS is related to variants in the *COL4A3- A4* and A5 genes that affect, respectively, the α3, α4 and α5 chains, which form trimers of type IV collagen. Given the impossibility of forming a α3, α4, α5 (IV) network in the glomerular basement membrane (GBM), this is replaced with a α1, α1, α2 (IV) network, which is insufficient to maintain normal glomerular permeability.[3,4] These alterations are non-specific and cannot be identified by electron microscopy, are by light microscopy it is common to observe a pattern of non-specific chronic glomerulonephritis (FSGS).[5,6]

The pathological diagnosis requires specific immunohistochemical techniques that can identify the absence of the Alport epitope in GBM, which can be suspected in electron microscopy, where the basement membranes become globally thinned resembling tramway tracks.[7,8] These techniques are not used routinely, as in our case with no family history. Therefore, we suspected that the diagnosis of FSGS could correspond to AS or other pathologies.

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A genetic study helps the diagnosis and can be performed early and with normal renal function, which is more convenient; it could be performed later, when the techniques for renal replacement treatment are required. Furthermore, it has the advantage of avoiding the risks associated with the renal biopsy itself and with the administration of unnecessary immunosuppressive treatments, as it happened in our case.

A better knowledge of the genetic variants associated with hereditary CKD will serve to: (1) define the phenotype-genotype relationship and establish the prognosis of the disease[6]; (2) facilitate the patient's participation in future clinical trials;[3,9,10] and (3) allow couples to have access to reproductive techniques and prevent the transmission of the disease to their offspring such as, preimplantation genetic testing (PGT) and gamete donation.[11,12]

In summary, achieving the correct diagnosis of hereditary CKD is an urgent need in the healthcare of the 21st century. A genetic study using NGS panels and an adequate family study with its corresponding genogram will allow to define the true magnitude of the disease, propose preventive reproductive measures and put our patients in the best condition to be able to participate in future clinical trials.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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