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Case report

A new mutation in the PAX2 gene in a Papillorenal Syndrome patient

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ABSTRACT

Purpose: To present a new mutation in a patient with Papillorenal Syndrome (PAPRS).
Observations: PAPRS is an autosomal dominant disease that involves ocular and renal abnormalities. We present a patient with PAPRS with a genetically diagnosed PAX2 and new pathogenic mutation. A complete ophthalmological, neurological, nephrological and Ears-Nose-Throat (ENT) examination were undertaken. The patient suffered from Focal Segmental Glomerulosclerosis (FSGS) and some typical ophthalmological signs of PAPRS, including optic nerve coloboma and optic disc pit (ODP) maculopathy associated with an abnormal retinal vessel distribution and numerous cilioretinal arteries in the right eye. The left eye showed similar vessel abnormalities although the optic disc had a normal morphology.
Conclusions: A new mutation in the PAX2 gene was identified in a patient with ocular and renal abnormalities.

1. Introduction

The background history of Papillorenal Syndrome (PAPRS) has been described in the literature and in previous reviews.[1] Formerly known as renal-coloboma syndrome, PAPRS is a mendelian autosomal dominant disease (OMIM: 120330) that involves ocular and renal abnormalities in addition to ENT, Central Nervous System (CNS), skin, and metabolic associations. This syndrome was first described in 1988 by Weaver et al.[2] in two siblings with optic disc colobomas associated with stage 5 chronic kidney disease. Nevertheless, the association of kidney failure and optic nerve abnormalities was already described by Rieger et al.[3] reporting a patient with optic nerve, retinal vessel and macular abnormalities associated with familial renal hypoplasia. Karscher et al.[4] also reported two cases of hereditary Morning Glory Syndrome and simultaneous shrinking of both kidneys. Later in the mid 90's, Sanyanusin et al.[5] reported a single nucleotide deletion in exon five of the PAX2 gene in a family with optic nerve colobomas and renal hypoplasia. This same author would then identify a mutation in the PAX2 gene in the case described by Weaver.[6]

In addition to optic disc coloboma and kidney hypoplasia, choroidal and vascular anomalies as well as other renal abnormalities such as polycystic kidney disease may be present in this syndrome. Both ocular and renal signs may be asymmetrical in the natural history of this syndrome hence making it a diagnostic challenge. Accurately diagnosing a patient with this condition requires multiple specialists' assessments. Mutations in PAX2 gene can be identified in 50% of patients with kidney and eye abnormalities suggestive of PAPRS. Point mutations in the coding region of PAX2 may not represent the only cause of PAPRS. However, most of the published cases of PAPRS have mutations in PAX2, thus biasing the information about the phenotype.[1] A multidisciplinary approach is needed to detect the many signs of this syndrome, making it a challenging diagnosis.

Our purpose is to present a PAPRS patient with a new genetically discovered PAX2 mutation.

2. Case report

We report a 14-year-old male patient that was referred to the nephrologist after an isolated finding of proteinuria (750mg/day) in the preoperative analysis before being operated on for cryptorchidism. The patient had phimosis and bilateral inguinal hernia as prior surgeries. There was no family history of renal abnormalities.

Serum creatinine levels and blood pressure were normal. Nonetheless, both kidneys were smaller when measured by ultrasound; the right kidney measured 85-mm and the left 83-mm. Normal kidney size ranges from 95mm to 110mm. A renal biopsy was then performed. The first biopsy showed absence of the glomeruli from both kidneys. The second test was held one year later, and the findings were segmental sclerosis with hyaline deposits and other zones with patches of glomerulomegaly. Thus, the diagnostic judgement was of Focal Segmental Glomerulosclerosis secondary to glomerulomegaly as an adaptive mechanism. The anatomical changes in the pedicel were

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scarce and most of the glomerulosclerosis findings were perihilar supporting this diagnosis. The blood pressure continued to increase until today's date. The treatment has aimed to reduce protein filtration using Renin-angiotensin system inhibitors and reducing protein and salt intake in the diet.

Throughout the renal follow up, the patient complained about decreased vision in the right eye and was therefore referred for a neuroophthalmological examination.

The Neurologists were the first to detect that the right optic disc was paler than the left optic disc. Pupil reflexes, external oculomotor movements, sensory and motor exploration, peripheral reflexes and the rest of the complete neurological exploration were normal.

When referred to the Ophthalmology department, a complete examination was undertaken. During the visit, the patient complained about reduced vision in the right eye, specifically about a central scotoma. The best corrected visual acuity (BCVA) of the right eye was 0.3 LogMAR and 0.0 LogMAR in the left eye. Anterior segment examination, pupillary reflexes, and external ocular eye movements were all normal. Intraocular pressure levels were in the normal range. Fundus examination of the right eye showed an optic disc pit (ODP) on the temporal aspect of the optic nerve head, optic disc coloboma, retinal vasculature with multiple cilioretinal vessels (Fig. 1a) and a perifoveal lesion associated with retinoschisis (Fig. 1b). Fundus examination of the left eye showed numerous cilioretinal vessels although the optic disc was normal.

In the Spectral Domain Optic Coherence Tomography (SD-OCT) (Cirrus, Carl Zeiss Meditec.) examination of the right eye, a severe retinoschisis of the outer nuclear layer underlying the entire macular area and a subfoveal neurosensory detachment correlated with the fundus exam and were compatible with ODP maculopathy (Fig. 2a and b). The OCT of the left eye showed no abnormalities.

The ODP maculopathy was first treated with topical dorzolamide in an attempt to reduce subretinal fluid. Subsequently, several surgical treatment options were considered as there was no significant improvement. A year later, the patient underwent a right pars plana vitrectomy (PPV), Internal Limiting Membrane (ILM) peeling, and fluid-gas exchange with C3F8. The macular architecture gradually improved (Fig. 3a) although there was no significant improvement in the BCVA.

Pax 2 mutation: Personal history of segmental focal glomerulosclerosis, arterial hypertension and ODP, raised suspicion of a possible PAPRS and a genetic study was requested to determine a possible PAX2 (10q24) mutation.

Peripheral blood samples were obtained. Genomic DNA was then extracted using *MagNA Pure* (Roche). The 12 coding exons of PAX2 gene where then amplified using specific PCR primers. Paired-end sequencing of 2 × 151pb was applied using the massive sequencer *MiSeq* (Ilumina). Sequencing libraries and purification were done using *Nextera XT* (Ilumina). Sequence variants were generated after alignment with the reference genome (UCSC hg19) using Burrows-Wheeler Aligner and the GATK variant caller. Amplimers were compared with Gene Bank Accesion Number NM_003987.3 as stated by the Genome Reference Consortium.

In the genetic sequencing results, a heterozygous nucleotide substitution was identified: c.418C > T, leading to a *missense* mutation p.(R140W) in the PAX2 gene. This is, a Cytosine substituted by Thymine in position 418 located in exon 4, resulting in a change in codon 140, codifying Tryptophan instead of Arginine.

This mutation has not been previously described in the literature. However, there is another *missense* mutation in the same amino acidic location c.419G > A p.(R1401), described in the *Human Gene Mutation Database (HGMD)*, access number CM068671 associated with renal dysplasia and no ocular abnormalities.

This probable pathogenic *missense* mutation may account for our patient's phenotype.

3. Discussion

As of today, there is no diagnostic criteria to define PAPRS. Schimementi et al.[7] described the ample phenotypical variability in four patients with identical PAX2 mutation and PAPRS. Iatropoulus et al.[8] also reported a high clinical variability in two monozygotic twins with the same PAX2 de novo mutation, one of them with optic disc coloboma and the other with no ocular abnormalities.

Most of the patients with this condition will present optic nerve and kidney abnormalities. Typical ocular findings are an enlarged optic disc with emerging peripheral vessels and cilioretinal vessels. Renal failure is present in most of the patients, mainly due to kidney hypoplasia. The Human Phenotype Ontology (HPO) database describes a list of the possible phenotypical associations that can be present in this syndrome.[9] Ocular findings vary from unilateral or bilateral optic nerve coloboma, retinal coloboma, chorioretinal atrophy, macular degeneration, lens luxation, macular hyperpigmentation, retinal detachment, cataracts, micropthalmos, retrobulbar cysts, optic nerve aplasia, ODP and morning glory anomaly.

As for the treatment options for ODP maculopathy, observation is a reasonable choice, especially in children, as spontaneous resolution has been reported.[10]

An initial approach may be the application of topical carbonic anhydrase inhibitors or laser photocoagulation. The latter was one of the first treatments described in an attempt to reduce the entrance of liquid into the macula. Nevertheless, BCVA is usually not recovered and visual field scotomas are often reported.[11]

Vitreomacular traction is a known factor in the pathophysiology of this entity. Therefore, pars plana vitrectomy is often the treatment of choice combined with ILM peeling or laser photocoagulation, and/or fluid-gas exchange. Although BCVA improvement is described in more than half of the cases,[12] our patient showed no recovery. Macular buckling has been largely abandoned as it is a difficult surgical

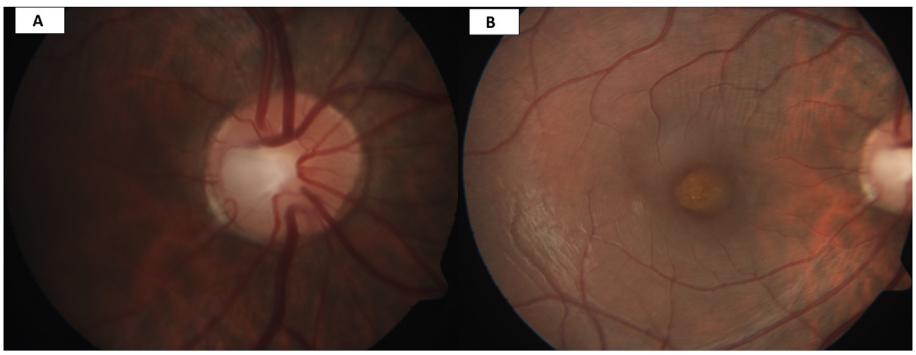

Fig. 1. 1a: Right eye fundus retinography showing ODP, numerous cilioretinal vessels and abnormal retinal vessel distribution. 1b: perifoveal yellowish lesion associated with retinoschisis.

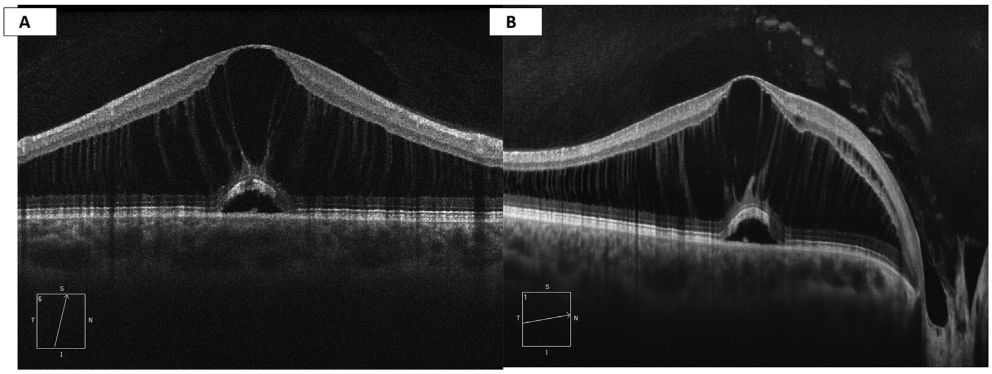

Fig. 2. 2a: ODP maculopathy showing severe retinoschisis affecting the outer nuclear layer and the nasal sector of the inner nuclear layer in practically the whole macular area. Neurosensory detachment is evident. 2b: notice the ODP.

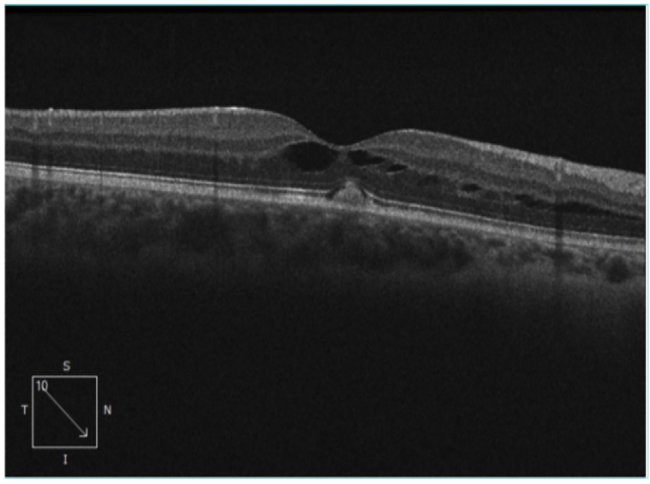

Fig. 3. Significant improvement of neurosensory detachment and retinoschisis with residual intraretinal fluid.

technique with a lengthy learning curve.[12]

Renal anomalies typically consist of hypoplasia associated with other genitourinary abnormalities such as horseshoe kidney, renal malrotation, vesicoureteral reflux, multicystic kidney dysplasia, renal cysts, and ultimately end stage renal failure. Nervous system abnormalities include mental retardation, seizures, gliosis and Arnold-Chiari type 1 malformation. Other rare findings may be present such as hyper extensible skin, joint laxity and sensorineural hearing impairment.

Several syndromes are characterised by ocular and renal abnormalities. Differential diagnosis includes CHARGE syndrome (coloboma, heart malformations, atresia choanae, retardation of growth, genital anomalies, ear and hearing abnormalities), COACH and Joubert Syndrome.[1]

PAX genes are essential for the regulation and control of patterning of the cells. Its name derives from Paired Box Gene, located in the amino terminal portion of the protein and consisting of a 128 amino acid domain.[13]PAX2 gene is one of the nine PAX paired box genes that encodes a DNA binding protein which is mainly expressed in the early embryogenic developing of the eye, CNS, ear and urogenital tract.[14] Specifically, PAX2 is expressed in the optic and otic vesicles, mesonephros, kidney, spinal cord, midbrain and hindbrain as it has been analysed in mice.[15] It maps to chromosome 10q24.3–10q25 containing 12 exons and four domains[16]: a paired domain, octapeptide domain, homeodomain and the transactivation domain. The paired domain has DNA binding properties and most pathogenic mutations are located here. Similarly, the homeodomain also seems to have DNA binding properties and most of the mutations in this domain are nonsense.[17] Bower et al.[17] recently reported more than 170 cases of PAPRS, with only half of them presenting PAX2 mutations. Most of the pathogenic mutations are located in the paired domain encoded by exons,[2–4] being c.77dupG the most common. Apart from PAX2 gene, kidney and eye development is regulated by a complex network of genes, including GDF11, GDNF, FOXC1, SIX1, SALL1, PAX8, and WT1.[18] Mutations in genes other than PAX2 may contribute to the pathogenesis of PAPRS.[19] Recently Okumura et al.[19] described a novel pathogenic mutation in KIF26B in a patient with clinical manifestations of PAPRS. This study group also observed that ocular and renal involvement was more severe in PAPRS patients with PAX2 mutations. Optic disc coloboma was classified into four scores: score 0, normal optic disc; score 1, optic disc dysplasia with unusual retinal and cilioretinal vessels; score 2, ODP and the findings in score 1; score 3, large coloboma involving the whole surface of the optic disc; score 4, optic disc coloboma and adjacent retina. Patients with PAX2 mutations had higher scores than those without PAX2 mutations. Similarly, patients with PAX2 mutations had higher urinary protein excretion and lower estimated glomerular filtration rates than those without PAX2 mutations. Nevertheless, patients with identical PAX2 mutations showed different kidney and ocular abnormalities and were different in the severity of the symptoms.[19]

Knowing that PAX2 is a protein transcription factor that plays a critical role in the formation of the eye and the kidney during embryogenic development, patients with isolated ocular or renal abnormalities should be assessed by ophthalmologists and nephrologists, and genetic testing for PAX2 mutations should be performed.

We present a case of a unique mutation in a previously unknown locus in the PAX2 gene in a patient with PAPRS and suggest it may be included in the locus specific mutation database for PAPRS.

Limitations of this study include regions that have not been analysed in PAX2 gene or those that might have not been detected by the technique that has been used.

Patient consent

Consent to publish this case report has been obtained from the patient in writing. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases)

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Declaration of competing interest

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