



# Renal Coloboma Syndrome—An Autosomal Dominant Genetic Disorder

S. Shanmuga Jayanthan<sup>1</sup> Rajagopal Ganesh<sup>2</sup> Narayanan Karunakaran<sup>2</sup> T. Mukuntharajan<sup>2</sup>  
A. Nancy Manodoss<sup>2</sup> Karan Dedhia<sup>2</sup> K. Nadasadharam<sup>1</sup>

<sup>1</sup>Department of Radiology, Meenakshi Hospital, Tanjore, Tamil Nadu, India

<sup>2</sup>Department of Radiodiagnosis, Meenakshi Mission Hospital and Research Centre, Madurai, Tamil Nadu, India

Address for correspondence S. Shanmuga Jayanthan, DNB, MNAMS 27, Third Cross Street, Subbaiya Pillai Nagar, Ammal Sathiram, Karaikal 609 604, Pondicherry, India (e-mail: jettan.32@gmail.com).

Indian J Radiol Imaging 2023;33:260–263.

## Abstract

### Keywords

- ▶ optic nerve dysplasia
- ▶ papillorenal syndrome
- ▶ renal coloboma syndrome

Renal coloboma syndrome is an autosomal dominant genetic disorder that primarily affects kidney and eye development. It is also known as papillorenal syndrome. People with this condition typically have kidneys that are small and underdeveloped (hypodysplastic), which can lead to end-stage renal disease. It has been estimated that approximately 10% of children with hypoplastic kidneys may have renal coloboma syndrome. The eye anomalies consist of a wide and dysplastic optic disk with the emergence of the retinal vessels from the periphery of the disk, frequently called optic nerve coloboma.

## Introduction

Renal coloboma syndrome (RCS) also known as papillorenal syndrome describes a condition consisting of optic nerve dysplasia and renal malformations. The inheritance pattern is autosomal dominant. The first description of RCS was made by Weaver et al in 1988 in two brothers who had end-stage kidney disease (ESKD) with interstitial nephritis and optic nerve colobomas.<sup>1</sup> Later in 1995, autosomal dominant mutations in the transcriptional regulator, paired box 2 (PAX2), were identified in the family.<sup>2</sup> Apart from optic nerve coloboma, other associated ocular findings may include a small corneal diameter, retinal coloboma, scleral staphyloma, optic nerve cyst, and pigmentary macular dysplasia.<sup>3</sup> Apart from hypodysplastic kidneys, other associated renal anomalies include multicystic dysplastic kidney and horseshoe kidney.<sup>4</sup> Here, we present a case of 16-year-old male with complaints of right eye blindness and renal failure.

## Case Report

A 16-year-old male patient presented with complaints of bilateral periorbital swelling and decreased urine output since 2 months. The patient also had complaints of loss of vision in the right eye since 6 years, evaluated and diagnosed with optic disk coloboma extending to the optic nerve (right > left). There was no family history of similar problems and renal dysfunction. On examination, the patient had pallor. Blood pressure, pulse, respiratory rate, and oxygen saturation were within normal limits.

Laboratory investigations revealed elevated serum creatinine (15.5 mg/dL) and blood urea (223 mg/dL) suggestive of renal failure, and reduced hemoglobin (5.0 g/dL), normal serum iron (77 µg/dL), elevated total iron binding capacity (206 mg/dL), and elevated serum ferritin (1276 ng/dL) suggestive of anemia of chronic disease.

B-mode ultrasound of the abdomen was done which revealed bilateral contracted kidneys (right measures

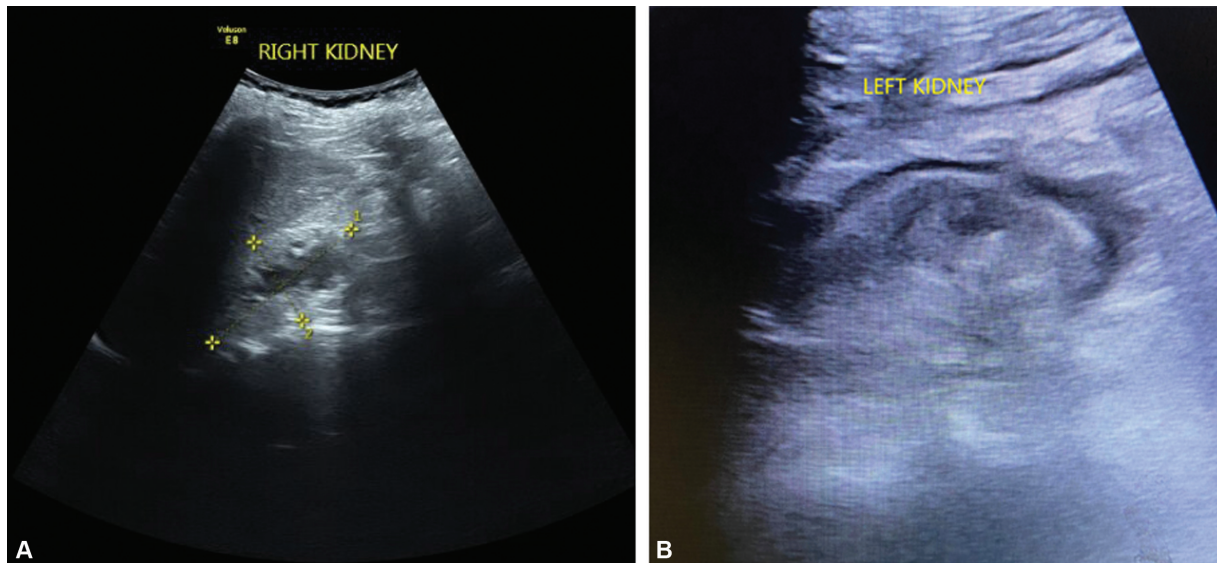
article published online  
January 6, 2023

DOI <https://doi.org/10.1055/s-0042-1760282>.  
ISSN 0971-3026.

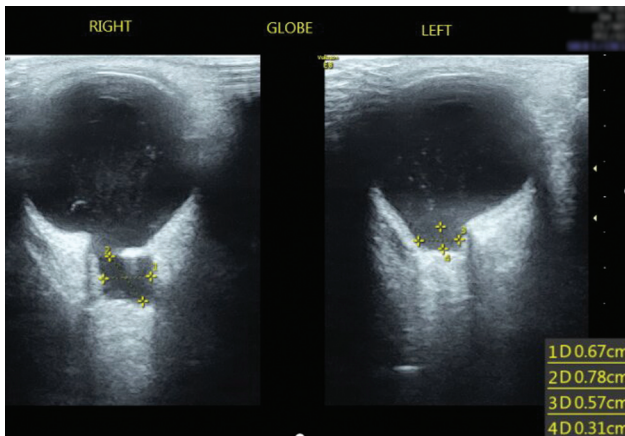
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**Fig. 1** (A and B) B-mode ultrasound shows contracted right and left kidney with renal cortical echos equal to that of renal sinuses.



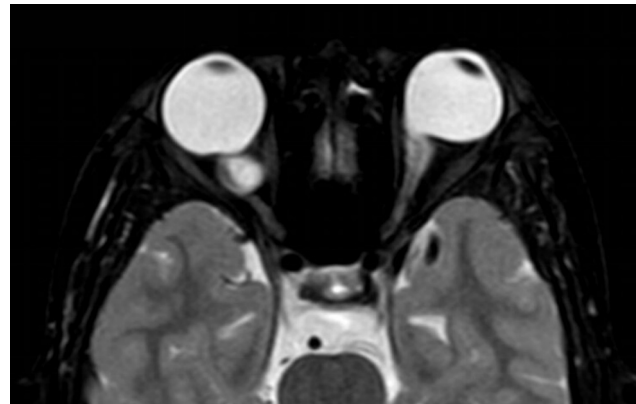
**Fig. 2** Ultrasound of both orbits revealed defect in the posterior aspect of globes at the level of insertion of optic disk.

5.8 × 3.0 cm and left measures 5.5 × 3.2 cm) with renal parenchymal echogenicity equal to that of renal sinuses suggestive of bilateral grade 3 renal parenchymal changes (► **Fig. 1A and B**).

B-mode ultrasound of both orbits (► **Fig. 2**) revealed the defect in the posterior aspect of the globe at the level of insertion of the optic disk head showing herniation of vitreous with a defect measuring 0.67 cm in width and 0.78 cm in depth on the right side and 0.57 cm in width and 0.31 cm in depth on the left side.

Magnetic resonance imaging (MRI) of orbits revealed a smaller size of the right globe with a focal posterior defect at the level of optic disk forming a retrobulbar fluid cyst with vitreous herniation within. A focal posterior defect at the level of optic disk was also noted on the left side. MRI brain revealed no associated midline or skull base anomalies (► **Figs. 3 and 4**).

Optical coherence tomography of orbit revealed retino-choroidoscleral excavation with a fine layer of retina cover-



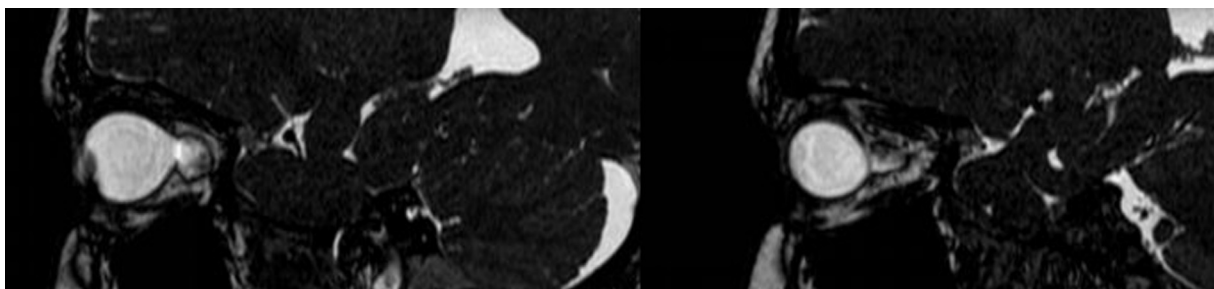
**Fig. 3** Axial T2 SPIR sequence of orbits shows a focal posterior defect at the level of optic disk forming a retrobulbar fluid cyst with vitreous herniation within noted on the right side. A focal posterior defect at the level of optic disk also noted on the left side suggestive of optic disk coloboma.

ing the sclera with cystoid edema temporal to optic disk coloboma.

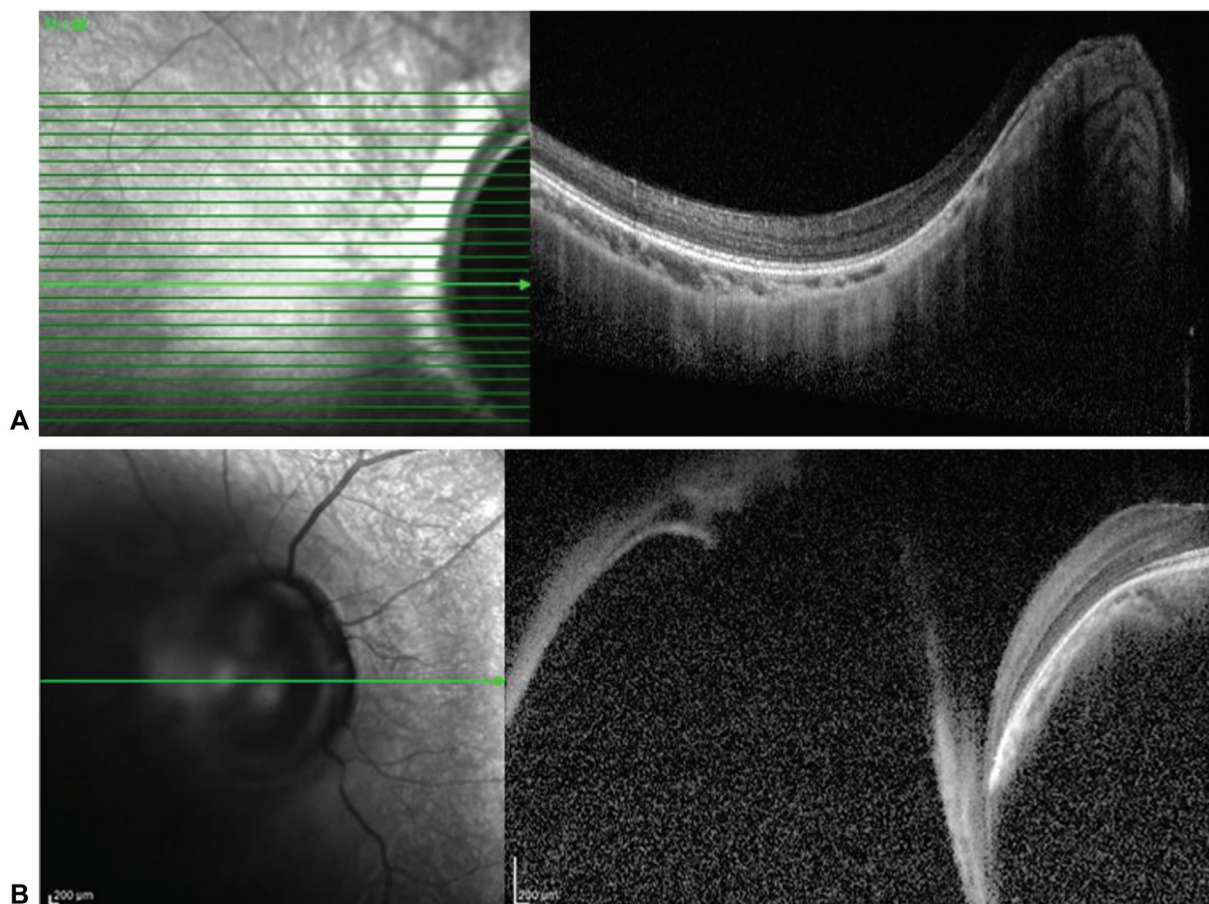
Based on the clinical features, laboratory investigations, and imaging findings, the patient was diagnosed to be a case of renal coloboma syndrome with end-stage renal disease. Attendees were informed about genetic testing, but since it would not change the medical management and due to financial constraints, testing was denied. The patient parents were counseled about the need for a renal transplant in view of the need for long-term hemodialysis.

## Discussion

RCS is an autosomal dominant disorder which shows wide inter- and intrafamilial variability. It is characterized primarily by ocular signs (77%) and renal manifestations (92%). The renal features are part of a spectrum of malformations termed congenital anomalies of the kidney and urinary tract



**Fig. 4** Sagittal FFE sequence of brain shows a focal posterior defect at the level of optic disk forming a retrobulbar fluid cyst with vitreous herniation within noted on the right side. A focal posterior defect at the level of optic disk also noted on the left side suggestive of optic disk coloboma.



**Fig. 5** (A and B) Optical coherence tomography images in show a fine layer of retina covering the sclera with cystoid edema.

(CAKUT).<sup>5</sup> To date, *PAX2* mutations have been the only identified genetic cause associated with RCS.

*PAX2* gene, located on chromosome 10q24, is a member of paired box transcription factor family and is one of the most critical genes involved in the human urinary system and eye development.<sup>6,7</sup> One study showed that 10% (2 out of 20) of patients with urinary tract malformation who underwent kidney transplantation possessed the *PAX2* mutation.<sup>5</sup> Another study in Japan concluded that 6.5% (38 out of 457) of patients with CAKUT carried the *PAX2* mutation.<sup>6</sup> Since the renal disease is identified in 92% of mutated individuals, and eye disease in 77% of individuals implies that the disorder is highly penetrant.<sup>8</sup>

The most common renal manifestation is renal hypodysplasia, which is usually bilateral and presented in 65% of involved individuals.<sup>9</sup> Other renal abnormalities include renal insufficiency, cystic kidney disease, vesicoureteral reflux (VUR), and other CAKUT. Histologically, the kidneys show less than a normal number of glomeruli with glomerular hypertrophy indicative of oligomeganephronia.<sup>10</sup> Eye abnormalities include optic nerve dysplasia and coloboma, which comprise around 72% of patients, and other findings include retinal coloboma, optic nerve cyst, macular abnormalities, or lens abnormalities.<sup>8</sup> Consequences of the renal hypodysplasia include hypertension, proteinuria, and renal insufficiency that frequently progresses to ESKD. Consequences of the ocular

malformations include decreased visual acuity, blindness, and retinal detachment. Reported nonrenal and nonophthalmological manifestations include high-frequency sensorineural hearing loss (7%), short stature, developmental delay, autism, CNS malformations (e.g., Chiari I malformation), hyperuricemia, soft skin, joint laxity, elevated pancreatic amylase, and short digits.<sup>11</sup> The correct genetic diagnosis is crucial for guiding clinical management and genetic counseling, especially in familial cases.

Management of the disease should be focused on preventing ESKD and vision loss. Strategies include blood pressure control, treatment of VUR, avoidance of nephrotoxic drugs, and prevention of retinal detachment. Renal replacement therapy is recommended and vision experts may provide assistance to adapt to continued vision loss.

Prenatal testing is another possibility for prevention or awareness, and this can be done through molecular genetic testing. Additionally, preimplantation genetic diagnosis should be considered for families known to have papillorenal syndrome.

The differential diagnosis for renal coloboma syndrome includes CHARGE syndrome (coloboma, heart malformations, atresia choanae, retardation of growth and development, genital anomalies, and ear and hearing abnormalities), craniofacial or cognitive abnormalities which are typical of CHARGE syndrome are absent. In patients with *PAX6* mutations eye findings may overlap, but renal anomalies are lacking. Patients with Joubert syndrome can have both colobomas and renal dysplasia; however, developmental disability, cerebellar hypoplasia, and cerebellar dysfunction are absent in RCS.

#### Conflict of Interest

None declared.

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