Clinical Vignette

Leber Congenital Amaurosis: Need for an Eye for Detail Beyond the Eye

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Abstract

A 10-year-old female child presented to our outpatient department with complaints of diminution of vision in both eyes since birth. On evaluation, she had reduced distant visual acuity in both eyes with no refractive correction and absent pupillary responses. Pendular nystagmus was present, and fundus examination revealed pigmentary nummular lesions at the level of retinal pigment epithelium (RPE) with sub-retinal flecks in the peripheral fundus. Electroretinogram revealed extinguished response and a clinical diagnosis of Leber congenital amaurosis (LCA) was made. On further evaluation she was found to have pallor with failure to thrive and short stature and investigations revealed anemia with deranged renal functions. Possibility of a ciliopathy was thought of due to eye and renal involvement. This was confirmed by whole exome sequencing performed after due counseling of the parents which revealed a pathogenic homozygous nonsense variant in the *IQCB1* gene (NM_001023570; c.1504C>T). Pathogenic variants in *IQCB1* are associated with Senior-Loken syndrome 5 and Leber congenital amaurosis with or without renal disease. Leber congenital amaurosis is a genetically heterogeneous condition. Pathogenic variants in some genes like *IQCB1* are associated with renal disease besides ocular involvement. Comprehensive evaluation by an ophthalmologist along with a clinical geneticist and nephrologist are essential in LCA patients as early intervention improves prognosis and clinical outcome.

Keywords: Leber congenital amaurosis, Senior-Loken syndrome 5, *IQCB1* mutation, chronic kidney disease.

Introduction

Leber congenital amaurosis encompasses a spectrum of inherited conditions that cause subnormal vision. The chief manifestation is bilateral congenital blindness, with diminished or absent electroretinogram (ERG) before the age of six months. Wide clinical and genetic heterogeneity is known with more than 20 genes of LCA reported to date. Many children have systemic manifestations apart from blindness which may be subtle initially but are gradually progressive including nephronophthisis and chronic kidney disease (CKD). Renal involvement is reported with certain genetic subtypes of LCA (e.g., *IQCB1-*, *IFT140-*, and *CEP290*-associated LCA) as part of syndromes including Senior-Loken syndrome and Joubert syndrome (Braun et al., 2016; König et al., 2017). Thorough history taking and physical examination along with focussed biochemical and radiological investigations can help in timely identification, confirmation of molecular diagnosis and institution of supportive management in patients with this rare genetic disorder. We report a case of ten-year-old girl who presented with diminution of vision who was suspected to have LCA with juvenile nephronophthisis based on history and clinical examination. Whole exome sequencing (WES) showed a pathogenic variant in the *IQCB1 gene* which helped us clinch the diagnosis.

Figure 1 1a: Fundus photographs of both the eyes showing pigmented nummular lesions at the level of the retinal pigment epithelium (RPE)

Patient details:

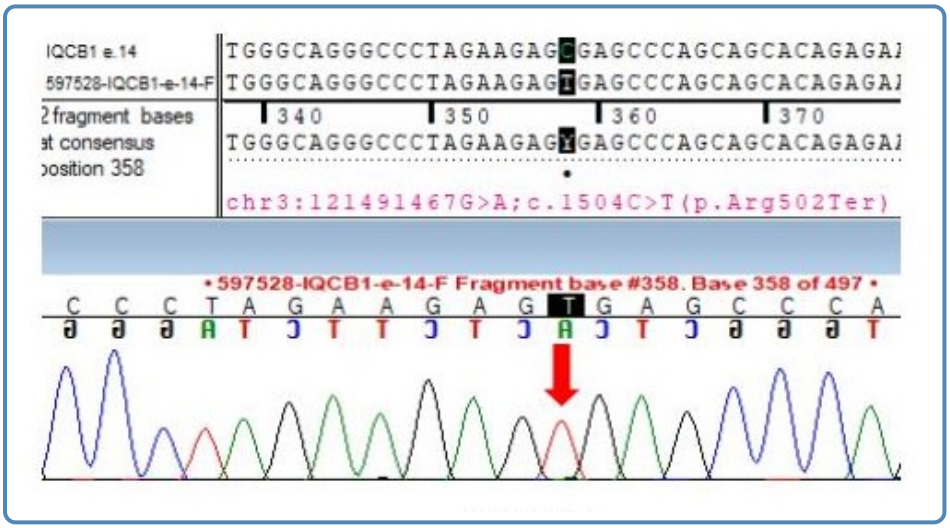
A ten-year-old female child, first born out of non-consanguineous marriage, was brought to the ophthalmology outpatient department of our institute with complaints of diminution of vision in both eyes since birth. The antenatal and birth history was unremarkable. She achieved developmental milestones as per age. On direct questioning parents confirmed that they had noticed polyuria and polydipsia since last 4-5 years along with poor weight and height gain as compared to her peers. There was no history suggestive of any other systemic involvement. The parents also reported similar eye complaints in their three-year-old daughter; the second daughter was unaffected as per the given history.

The ophthalmological findings of the proband at initial presentation are mentioned in **Table 1. Figure 1a** shows the significant eye findings seen in the proband.

Based on the above, the child was diagnosed to have Leber congenital amaurosis (LCA) and referred to the pediatric nephrology OPD for further evaluation. On examination there, the child was found to have weight of 22 kg and height of 118 cm (both <3 SD for age) and was normotensive for her age. Head to toe examination revealed eye signs as elucidated above along with pallor. The systemic examination was essentially normal. She had no focal neurological deficits, and her hearing examination was also normal. Investigations confirmed anemia (normocytic normochromic) and hypocalcemia along with deranged renal function with estimated glomerular filtration rate (eGFR) commensurate with chronic kidney disease (CKD) stage 3b. The investigation results are summarized in **Table 2**. The child was put on medical management for the same. Based on history, clinical examination findings and initial investigations, a diagnosis of a ciliopathy like Senior-Loken syndrome was suspected and opinion of the clinical geneticist was sought.

Parents were counseled and to confirm the diagnosis, exome sequencing was performed on genomic DNA with analysis of medically relevant genes listed in OMIM (https://www.omim.org/). A homozygous nonsense variation in exon 14 of the *IQCB1* gene (NM_001023570; chr3:g.121491467G>A; c.1504C>T) that results in a stop codon and premature truncation of the protein at codon 502 (p.Arg502Ter) was detected. This variant is classified as pathogenic as per the guidelines of the American College of Medical Genetics and Genomics (ACMG). The variant was further validated by Sanger sequencing (**Figure 1b**). Careful clinical association was done, and she was diagnosed as a case of Senior-Loken syndrome-5. This is a disorder characterized by nephronophthisis and Leber congenital amaurosis.

The elder of her other two siblings, a five-year-old girl, had no features of nephronophthisis or Leber congenital amaurosis. The younger one, a three-year-old girl, had features of amaurosis with depigmented fundus in both eyes. However, she had no features suggestive of renal involvement. Sanger



1b: Sanger sequence chromatogram showing the c.1504C>T variant in the *IQCB1* gene in the proband

sequencing confirmed the presence of the same variant in homozygous form in the youngest sibling, while the unaffected sibling and parents were confirmed to be asymptomatic heterozygotes. Parents were counseled about the autosomal recessive pattern of inheritance and the 25% risk of recurrence in each offspring. The importance of prenatal diagnosis in subsequent pregnancies was emphasized.

Discussion

We report a 10-year-old girl who presented with diminution of vision, whose ophthalmological evaluation showed all features of LCA including poor fixation at birth or within 6 months of age, nystagmus, amaurotic pupils, and extinguished ERG response before the age of 1 year. A thorough history however pointed towards other system involvement prompting a detailed multispecialty evaluation by a clinical geneticist and pediatric nephrologist which revealed features of nephronophthisis with CKD stage 3. Molecular confirmation of the clinical diagnosis was done by exome sequencing which demonstrated a homozygous nonsense variant in the *IQCB1* gene (NM_001023570; c.1504C>T) associated with Senior-Loken syndrome (SLNS). Leber congenital amaurosis is a clinically and genetically heterogenous condition. More than 20 genes are associated with this condition. LCA may be part of a 'ciliopathy syndrome' also known as NPHP-related ciliopathies (NPHP-RC) with associated multisystem involvement primarily affecting the nervous system, eye, renal and skeletal system like Joubert syndrome; renal system involvement like Senior-Loken syndrome; cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis i.e., COACH syndrome; or be present as an isolated entity. Exact genotype-phenotype correlation has not been elucidated and with increasing confirmation of molecular diagnosis by next generation sequencing (NGS), varied phenotypes of described mutations continue to emerge (den Hollander et al., 2008). Mutations in the *NPHP1* gene have been reported to have predominantly renal manifestations with progression to CKD stage V by early adolescence though some patients may also have neurological and eye signs. In contrast, mutations in the *IQCB1* gene, which is also involved in ciliogenesis, manifest with LCA in early childhood. Renal symptoms are seen only in about half of the affected patients with relatively late progression to CKD stage V and few may also have neurological involvement (König et al., 2017; Kang et al., 2016; Wolf et al., 2024). In our patient, the eye signs appeared in early infancy and renal involvement was picked up only at 10 years of age by a focussed evaluation before the parents had noticed the same which has been reported earlier in patients with underlying mutations in the *IQCBI* gene (König et al., 2017). Diagnosis of nephronophthisis may be delayed as in early stages the patients have only mild symptoms which may go unnoticed and hence it is imperative that all LCA patients should be evaluated thoroughly for possible renal and other

Table 1 Ophthalmological examination of proband at initial presentation

	Right eye	Left eye
1. a. Visual Acuity b. Color vision c. Intraocular pressure	1/60 Unable to read any slides 16 mm of Hg	1/60 Unable to read any slides 18 mm of Hg
2. Anterior and posterior segment examination	a. Nystagmus + b. Absent pupillary response c. Pigmentary nummular lesions at the level of RPE with sub-retinal flecks in the peripheral fundus.	a. Nystagmus + b. Absent pupillary response c. Pigmentary nummular lesions at the level of RPE with sub-retinal flecks in the peripheral fundus.
3. Ophthalmological investigations a. Electroretinogram b. Fundus autofluorescence c. Optical Coherence Tomography (OCT) Macula	 Extinguished response Hypo-autofluorescence in the macular region Central macular thickness (CMT) 249 microns	 Extinguished response Hypo-autofluorescence in the macular region Central macular thickness (CMT) 266 microns

Table 2 Summary of Investigation Results of the Proband

Parameters	Value in Our Patient	Normal Range
Hemoglobin - 9.4 gm% Peripheral blood smear	9.4 gm% Normocytic normochromic anemia	12-13 mg/dL
Serum urea Serum creatinine	52.9 mg/dL 1.32 mg/dL	20-40 mg/dL 0.4-0.9 mg/dL
Calcium Organic phosphorus Alkaline phosphatase	5.8 mg/dL 5 mg/dL 655 IU/L	8.5-9.5 mg/dL 3-4.5 mg/dL 40-140 IU/L
Serum iron Total iron binding capacity (TIBC)	114 mcg/dL 390 mcg/dL	60-170 mcg/dL 240-450 mcg/dL
iParathormone 25-OH Vitamin D3	301 pg/mL 15 ng/mL	14-65 pg/mL 15-45 ng/mL
Ultrasound of kidneys, ureter and bladder (USG KUB)	Raised echogenicity of both kidneys; cortico-medullary differentiation normal. Kidney sizes: right kidney 7.3 cm, left kidney 7 cm	Normal kidney size for this age: 9.5-10 cm

system involvement.

Conclusion

Patients with LCA may have subtle extra-ocular manifestations. Thorough evaluation is essential in all patients as early intervention improves prognosis and clinical outcomes. Molecular confirmation of underlying genetic diagnosis helps in appropriate genetic counselling including prognostication and timely institution of supportive therapy of systemic involvement including CKD. It also aids in offering appropriate prenatal diagnosis to parents if planning further pregnancy which, is an important cog in the wheel of patient management in such cases.

Declaration of patient consent: The authors

certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/ have given his/ her/ their consent for his/ her/ their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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