

## Leber's Amaurosis with Nephronophthisis and Congenital Hepatic Fibrosis

Varinder Singh  
 Sabyasachi Bhattacharjee  
 Kirti Singh †  
 M.K. Narula\*

We describe a case of Leber's amaurosis in a one-year-old girl with unusual presentations. She presented with small clue like tachypnea and nystagmoid movement of eyes which when pursued revealed involvement like hepatic, renal and retina.

**Key words:** *Neurologic disorder, Rod-cone dystrophy.*

Leber's amaurosis is a rod-cone dystrophy, which presents at birth or in the first few months of life. It may be inherited as an autosomal recessive trait or even sporadic in many. It may be associated with other extra-ocular features, mental subnormality, neurological disorders, renal disease, sensori-neural hearing loss or congenital hepatic fibrosis(1). Renal involvement may be in the form of nephronophthisis, which is a very rare entity and exact incidence of which is not known. We did not find any published report from India on this entity through Medline search.

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*From the Departments of Pediatrics and Radiology\*, Lady Hardinge Medical College and †Maulana Azad Medical College and Associated Guru Nanak Eye Center, New Delhi 110 002.*

*Correspondence to: Dr. Varinder Singh, 200, Dhudial Apartments, Pitampura, Delhi 110 034.  
 Email: v.singh@ndf.vsnl.net.in*

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### Case Report

A one-year-old girl was admitted with mild to moderate, continuous fever, cough and cold for 3 days and breathlessness on the day of admission. Since the age of three months, the child was suffering from frequent, brief episodes of fever, loose motions, vomiting and breathlessness which responded to medications from local practitioner. There was no history of polyuria or polydipsia. She was not hospitalized in the past. There was history of wandering gaze, clumsy crude hand movements while reaching for objects and delayed development. The child was a product of a consanguineous marriage. There was no family history of similar illness in any first degree relative at that time. There was no fetal loss or sibling deaths in the past.

Antenatal and perinatal history was uneventful. The child had delayed milestones- as she achieved head holding at 5 months, sitting without support at 10-11 months, had no eye-to-eye contact and only vocalization was present at the age of 1 year. Hearing was normal. She had a wandering non fixating gaze, however she could reach out for objects when offered.

The child weighed 5 kg with head circumference of 40 cm and length of 69 cm (all parameters below 5th percentile for age) with proportionate upper segment to lower segment ratio (1.3:1). She was tachypneic (RR 54/min), febrile, well hydrated and normotensive (74/54 mm Hg). She had moderate pallor, blue sclera, nystagmoid movement of eyes with poor light fixation with bilateral dilated pupils with sluggish reaction to light. Skin and hair were of normal pigmentation. There was no cyanosis, icterus, edema, lymphadenopathy or clubbing. Chest and CVS examination were normal. Liver was palpable 4.5 cm below right subcostal margin,

firm in consistency, smooth surface and sharp borders. Spleen and kidneys were not palpable.

Investigations revealed a normocytic, normochromic anemia (Hb 6.5 g/dL). Urine analysis, culture and X-ray chest were normal. Acid base study revealed metabolic acidosis (pH = 7.192, BE = -20.5). Kidney function tests showed a blood urea of 83 mg/dL, S. Creatinine of 2.7 mg/dL with hypokalemia (2.7 mEq/L), hypocalcemia (6.9 mg/dL) and a normal serum sodium (141 mEq/L). LFT showed SGOT = 113 U/L and SGPT = 121 U/L with serum uric acid of 4.7 mg/dL. Her TORCH testing including VDRL, skeletal survey and hearing assessment did not reveal any abnormality.

Ocular examination revealed poor vision (6/60) with nystagmoid movements. Anterior segment was within normal limits. The child's retina had salt and pepper appearance *i.e.*, hypopigmentation with areas of hyperpigmentation. The disc and vessels were normal. No pigment clumping or corpuscles or optic disc abnormality was visible. Refraction under full cycloplegia revealed hypermetropia of + 4 Diopters(2). A positive tapetal reflex was also present. ERG revealed a decrease in amplitude of a and b waves. Oculodigital sign was not seen.

An ultrasound abdomen demonstrated that both kidneys had large medullary regions with thinning of cortex. The medulla showed multiple small cysts in a radiating pattern with few areas of increased echogenicity but no definite shadowing suggestive of calcification. The liver was also enlarged with normal texture. A liver biopsy showed hepatic fibrosis. Parents refused consent for kidney biopsy.

We looked at various associations of salt pepper fundus to explain all our findings. The

patient had no stigmata suggestive of intrauterine infection and serological tests (TORCH & VDRL) were negative so congenital toxoplasmosis, rubella and syphilis were ruled out. By exclusion of these and due to the presence of renal and hepatic dysfunction we diagnosed the patient as Leber's amaurosis.

The child responded to intravenous and oral supplements of sodium bicarbonate, potassium, calcium, hematinics; and was discharged after hypermetropic correction. She is on regular follow-up for over 1.5 years.

On follow-up, USG abdomen showed a shrinking kidney size associated with persistent but stable derangement of kidney functions. The child was asymptomatic till the last follow-up and was maintaining blood pH and electrolytes on the treatment given.

Incidentally, in spite of our counseling, the mother approached us when she was in the seven month of her next pregnancy. USG at this stage showed medullary cysts in bilateral fetal kidneys. Ultrasonographic findings have been confirmed postnatally in this female sibling which are similar to the previous child.

### Discussion

We are reporting this case not merely for its rarity but also because she presented with common symptoms of acute respiratory infection. However, it was the presence of small clues like tachypnea in the absence of any clinical and radiological chest findings, presence of nystagmoid movement of eyes which when pursued revealed significant involvement of systems like hepatic, renal and the retina.

Leber's amaurosis should be suspected in any infant with poor vision, nystagmus, sluggish pupil reactions with a normal or salt pepper type of fundus. An absent or severely

subnormal photopic and scotopic ERG confirms the diagnosis. Most cases of Leber's amaurosis occur in otherwise normal infants. However a variety of associated systemic abnormalities including mental subnormality, neurological disorders, renal disease and hearing loss, have been reported in association with it. It is likely that majority of these disorders are caused by different genetic mutation unrelated to that causing an isolated infantile rod cone dystrophy(3).

Mental retardation and neurological disease are the most frequent of the reported association. A hypoplasia of cerebellar vermis is seen in 10% infants of Leber's amaurosis(4). Sensory neural hearing loss occurs in about 5% of children with Leber's amaurosis(5). Renal abnormalities, particularly juvenile nephronophthisis have been reported earlier with Leber's amaurosis, but exact incidence is not yet known(6).

The Senior Loken Syndrome (SLS) represents the concomitant occurrence of nephronophthisis and retinitis pigmentosa. An early onset and a late onset variant of SLS have been described. In early onset type children present with coarse nystagmus and/or blindness at birth or within the first two years of life. Fundoscopic alterations are present in all SLS patients by the age of 10 years. The late onset is characterized by development of blindness during school age after preceding night blindness. In our patient there was an early onset diminution of vision(7). The finding of blue sclera in our case has not been reported in the past.

Nutritional anemia may be normocytic normochromic initially which manifested due to chronic infection and responded to hematinics. Subsequently, the baby required subcutaneous erythropoietin as the anemia was multifactorial in our case. The persistent

derangement of renal function and presence of metabolic acidosis suggested presence of a persistent renal abnormality.

USG revealed cysts in renal medulla suggesting either a diagnosis of Medullary Sponge kidney or else Medullary Cystic Disease-Juvenile Nephronophthisis (MCD-JN) complex. We could not confirm the diagnosis by renal biopsy, which was refused by the parents. Medullary sponge kidney was however ruled out because of shrinking kidney size in our case unlike an enlarged kidney, which is usually seen with Medullary sponge disease. Further MCD has an autosomal dominant trait and has a late age of onset while juvenile nephronophthisis has an early onset and autosomal recessive trait. In view of this we diagnosed the renal involvement as MCD-JN complex. The nephronophthisis-cystic medulla complex derives its name from the pathologic appearance of kidneys. It has association with abnormalities like Leber's amaurosis, skeletal abnormalities *e.g.*, cone shaped epiphysis (Saldinomainzer' syndrome)(8) and congenital hepatic fibrosis(9).

Overall prognosis of this condition is not good and most children develop end stage renal disease. Genetic counseling of the parents for future pregnancies is required. In utero the disease may be suspected by the presence of cysts in the corticomedullary region. Genetic diagnosis is possible by identifying NPHP gene located in chromosome 2q 12 - q13(10).

The presence of typical USG findings of renal involvement (MCD-JN), hepatic fibrosis and salt pepper fundus makes the final diagnosis of Leber's amaurosis with MCD-JN and hepatic fibrosis tenable in this patient. The present case once again emphasizes the importance of investigating small clues,

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which do not fit into usual features of common diseases.

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