

Low syndrome: Case report of a patient with a novel mutation in the *OCRL* gene

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Introduction

The oculocerebrorenal (*OCRL*) syndrome of Low is an X linked, multisystem disorder characterised by a triad of abnormalities in the eyes, the nervous system and the renal tubules¹. It is caused by a mutation in the *OCRL* gene which encodes an inositol polyphosphate 5-phosphatase. This enzyme has been detected on vesicular structures of the endosomal system and the Golgi complex, and plays a main role in cellular metabolism. The deficiency of this enzyme impairs the maturation of polarizing epithelium in neurons and glia, renal proximal tubule and lens². Prevalence of this syndrome has been estimated as 1 in 500,000³.

Case report

This baby boy was born of a non-consanguineous marriage in January 2013 at the Base Hospital, Kahawatta and bilateral cataracts were detected at birth. On the 4th day of life, baby was referred to the Eye Surgeon, Lady Ridgeway Hospital (LRH), Colombo. He underwent bilateral trabeculectomy at the age of 2 months. At the age of 1 week, baby was referred to the Department of Chemical Pathology for necessary biochemical investigations of cataract by the eye unit. There is a history of delayed milestones. His family tree (Figure 1) revealed his maternal cousin to share the clinical features.

On physical examination, his weight was 6.2 kg less than - 3SD), height was 64 cm (less than -3 SD) and head circumference was 45 cm (10th

centile). He had frontal bossing, flat nasal bridge, upward nystagmus, microcephaly, hypermobility of joints, hypotonia, severe global developmental delay and failure to thrive (Figure 2).

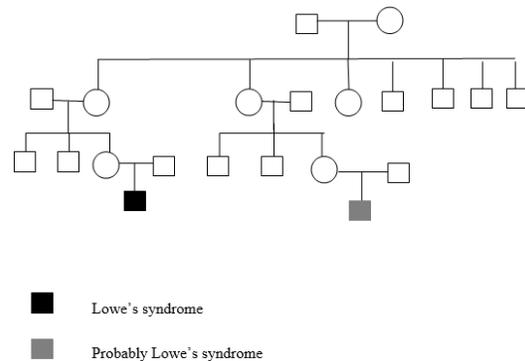


Figure 1: Family tree



Figure 2: Showing microcephaly, frontal bossing, flat nasal bridge and cataract

*Permission given by parents to publish photograph

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The clinical laboratory investigations showed hyperchloraemic metabolic acidosis with normal serum creatinine. Serum alkaline phosphatase, fasting phosphate, tubular reabsorption of phosphate and corrected calcium were 717 U/L (80 - 480), 1.06 mmol/L (1.45 - 2.16), 84% (> 85%) and 2.61 mmol/L (2.2 - 2.7) respectively. Serum creatine kinase, lactate dehydrogenase and aspartate aminotransferase were elevated. 25-hydroxy vitamin D level was 46.2 nmol/L (deficient ≤ 50) and parathormone (PTH) level was

66.5 pg/ml (10–65). His urine investigations are summarised in table 1. X-ray wrist showed delayed bone age. Ultra sound scan of the brain was normal.

Table 1: Urine biochemical investigations

Type of test	Result (ref. range)
<i>Spot test</i>	
pH	7.3 (6 - 6.5)
Uric acid: creatinine ratio (mmol/mmol)	1.64 (0.5 - 1.4)
Alanine (µmol/L)	7076 (767 - 6090)
Citrulline (µmol/L)	803 (22 - 181)
Lysine (µmol/L)	2760 (189 - 850)
Cystine	Positive
Tyrosine	Positive
Clinistix test for glucose	Negative
<i>24 hour excretion</i>	
Protein (mg/m ² /hour)	92 (<4)
Calcium (mmol/kg/day)	0.12 (<0.1)
Phosphate (mmol/kg/day)	0.7 (0.48 - 0.64)

He was treated with Joule’s solution and Polycitra. The clinical diagnosis of Lowe syndrome was confirmed by DNA analysis. This revealed a hemizygous mutation c. 1427C>T (p.Thr476Ile) in exon 14 and carriership was confirmed in the mother. Slit lamp examination of eyes of his mother did not reveal any abnormalities and her renal tubular functions were normal.

Discussion

Patients with OCRL syndrome, typically present in infancy with congenital bilateral cataract, growth failure and mental retardation. Cataract manifests early in embryogenesis. Congenital or childhood glaucoma has been observed in 50% of Lowe syndrome patients⁴. Neurologic manifestations include seizures, repetitive behaviour, intellectual disability and variable degree of mental retardation. Renal tubular dysfunctions include low molecular weight proteinuria, albuminuria, aminoaciduria, hypercalciuria and phosphaturia which may lead to chronic renal failure⁵.

Our patient was clinically diagnosed on the basis of typical oculocerebrorenal manifestations. Impaired proximal tubular reabsorption led to generalised aminoaciduria, proteinuria, phosphaturia, hyperuricosuria and metabolic acidosis. He did not have glycosuria which is consistent with other reported cases of Lowe and indicates selective proximal dysfunction in Lowe syndrome patients². Our patient also had vitamin D deficiency. Usually Lowe patients develop vitamin D dependent rickets due to impaired activation of 1-alpha hydroxylase with normal 25-hydroxy vitamin D level⁶. In our case vitamin D deficiency led to high PTH and ALP levels. X-rays did not show evidence of rickets.

Hyperphosphaturia and metabolic acidosis due to bicarbonate loss are part of the proximal tubulopathy of Lowe syndrome or result from PTH action on renal tubules. Hypercalciuria may be a manifestation of either tubulopathy or vitamin D deficiency. Though our patient had hypercalciuria, there was no radiological evidence of urolithiasis or nephrocalcinosis often reported in OCRL patients⁷. Severe hypotonia is reported in the literature³ and our patient also had hypotonia with elevated CK, LDH and AST despite of normal liver function. Elevation of these enzymes could be due to muscle involvement. According to the literature carrier mothers with a mild phenotype developed aminoaciduria following ornithine loading⁸ and often show eye lesions by slit lamp examination⁹. We could not perform ornithine loading test but eye examination did not detect any abnormalities. As she is a carrier, she has 25% of possibility of having an affected boy and 25% of possibility of having a carrier girl in future pregnancies. His 5-year-old cousin was clinically diagnosed as Lowe syndrome and is on treatment however we could not perform genetic analysis on him.

More than 200 mutations in the *OCRL* gene have been described in Lowe syndrome patients including nonsense, splice-site, missense mutations and insertions and deletions¹⁰. The missense mutation (c. 1427C>T) in exon 14 of the *OCRL* gene observed in our patient had not been previously reported. Probably it may be a novel mutation in Sri Lanka.

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