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Floppy Infant - Lowes Oculocerebrorenal Syndrome - Case Report

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Abstract: ***Lowe syndrome (the oculocerebrorenal syndrome of Lowe, OCRL) is a multisystem disorder characterised by anomalies affecting the eye, the nervous system and the kidney. It is a uncommon, panethnic, X-linked disease, with estimated prevalence in the general population of approximately 1 in 500,000[1]. Bilateral cataract and severe hypotonia are present at birth. In the subsequent weeks or months, a proximal renal tubulopathy (Fanconi-type) becomes evident and the ocular picture may be complicated by glaucoma and cheloids. Psychomotor retardation is evident in childhood, while behavioural problems prevail and renal complications arise in adolescence. The mutation of the gene* OCRL1 *localized at Xq26.1, coding for the enzyme phosphatidylinositol bisphosphate 5 phosphatase is responsible for the disease[2]. Both enzymatic and molecular testing is available for confirmation of the diagnosis and for prenatal detection of the disease. The treatment includes: cataract extraction, glaucoma control, physical and speech therapy, use of drugs to address behavioural problems, and correction of the tubular acidosis and the bone disease with the use of bicarbonate, phosphate, potassium and water. Also Mutations of the inositol-5-phosphatase OCRL cause Lowe syndrome and Dent-II disease. Both are rare genetic disorders characterized by renal defects.[4]***

Keywords: Lowe syndrome, phosphatidylinositolbisphosphate 5 phosphatase, oculocerebrorenal syndrome, floppy infant

1. Background

Tone is the resistance of muscle to stretch. Clinicians test two kinds of tone: phasic and postural. Phasic tone is a rapid contraction in response to a high-intensity stretch (deep tendon reflexes). Striking the patellar tendon briefly stretches the quadriceps muscle. The spindle apparatus, sensing the stretch, sends an impulse through the sensory nerve to the spinal cord. This information is transmitted to the alpha motor neuron, and the quadriceps muscle contracts (the monosynaptic reflex). Postural tone is the prolonged contraction of antigravity muscles in response to the low-intensity stretch of gravity. When postural tone is depressed, the trunk and limbs cannot maintain themselves against gravity and the infant appears hypotonic.

The maintenance of normal tone requires intact central and peripheral nervous systems. Not surprisingly, hypotonia is a common symptom of neurological dysfunction and occurs in diseases of the brain, spinal cord, nerves, and muscles. One anterior horn cell and all the muscle fibers that it innervates make up a motor unit. The motor unit is the unit of force. Therefore weakness is a symptom of all motor unit disorders. A primary disorder of the anterior horn cell body is a neuronopathy, a primary disorder of the axon or its myelin covering is a neuropathy, and a primary disorder of the muscle fiber is a myopathy. In infancy and childhood, cerebral disorders are far more common than motor unit disorders. The term cerebral hypotonia encompasses all causes of postural hypotonia caused by cerebral diseases or defects.[2]

In the early 1950s, Lowe and colleagues defined a new syndrome in children that included the classic features of intellectual disability, organic aciduria, decreased renal ammonia production, bilateral cataracts, and glaucoma. Since then, research has further characterized this disorder by identifying the presence of a Fanconi-type proximal renal tubulopathy, areflexia, and arthropathy. The oculocerebrorenal syndrome of Lowe syndrome is now known to be an X-linked recessive disorder impacting fundamental intracellular processes, explaining its multi-organ manifestations. Early diagnosis and supportive care are crucial to prevent life-threatening complications and maximize the quality of life[3].

2. Case Presentation

A term male infant (38 weeks) with birth weight of 3.4kg born to a G_2A_1 mother out of non-consanguineous marriage through vacuum assisted vaginal delivery , cried after gentle stimulation with thick meconium stained amniotic fluid. Following which baby had respiratory distress for which started on minimal oxygen by nasal prongs and weaned off oxygen over 12 hours in NICU.

Antenatal – spontaneous conception, booked case, taken 2 doses of inj. Td, all scans done and were normal, quickening felt at 5thmonth, perceived fetal movements well. A_1- spontaneous abortion in first trimester 1 year back.

No feeding or swallowing difficulty, ptosis, contractures, seizures, organomegaly, hypoglycaemic episodes.

On examination- Non sick baby , hypotonic with bilateral congenital cataract with micrognathia with absent lingual frenulum, hyporeflexia + , bilateral distal muscle wasting + , joint hyperflexion + Neurosonogram- showed grade 1 germinal matrix bleed which resolved on subsequent scan , bllod investigations showed raised CPK levels (1968 U/L) , USG abdomen- normal.

On day 4 of life blood sample sent to whole exome sequencing which is positive for loweoculocerebrorenal syndrome reports attached below. Following which baby was discharged on day 7. On regular follow up there is mild motor delay with hypotonia of limbs and renal function tests are normal.

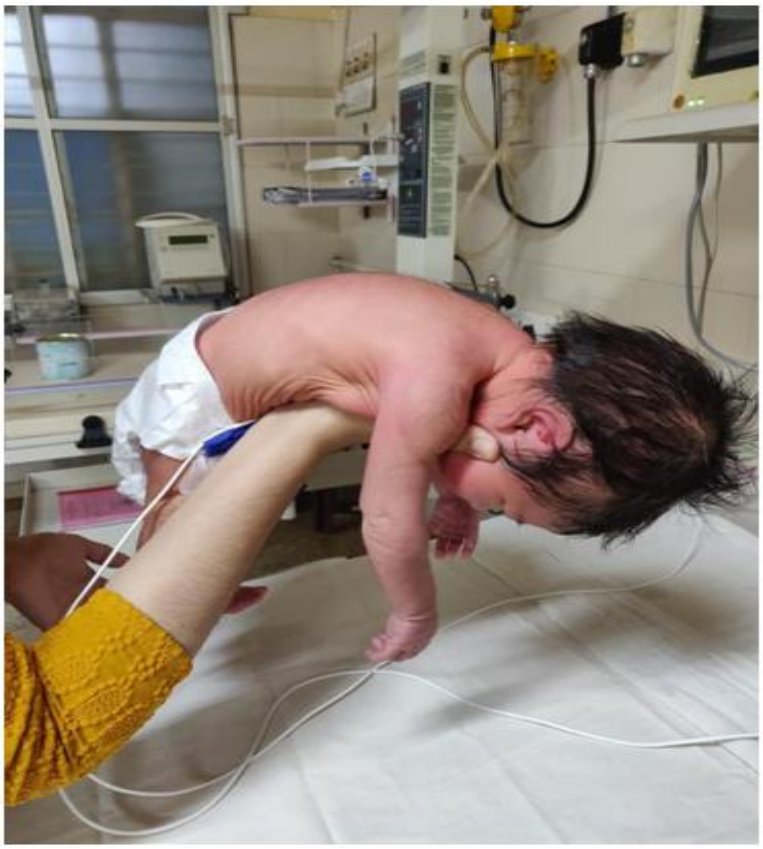


Figure 1: Ragged doll sign on ventral suspension due to hypotonia

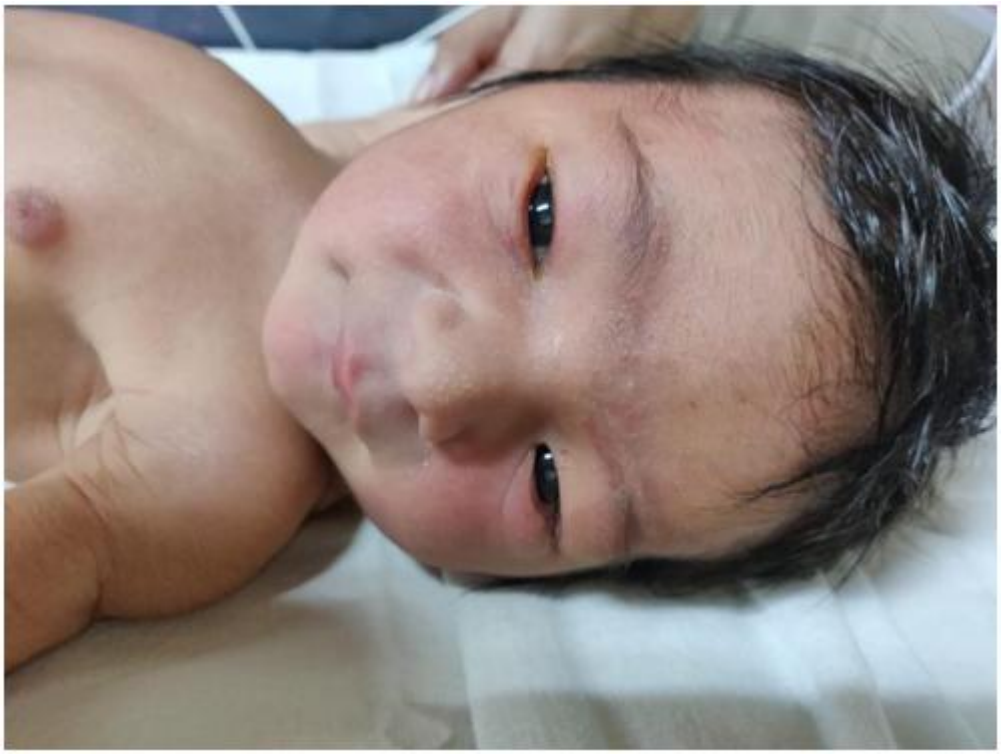
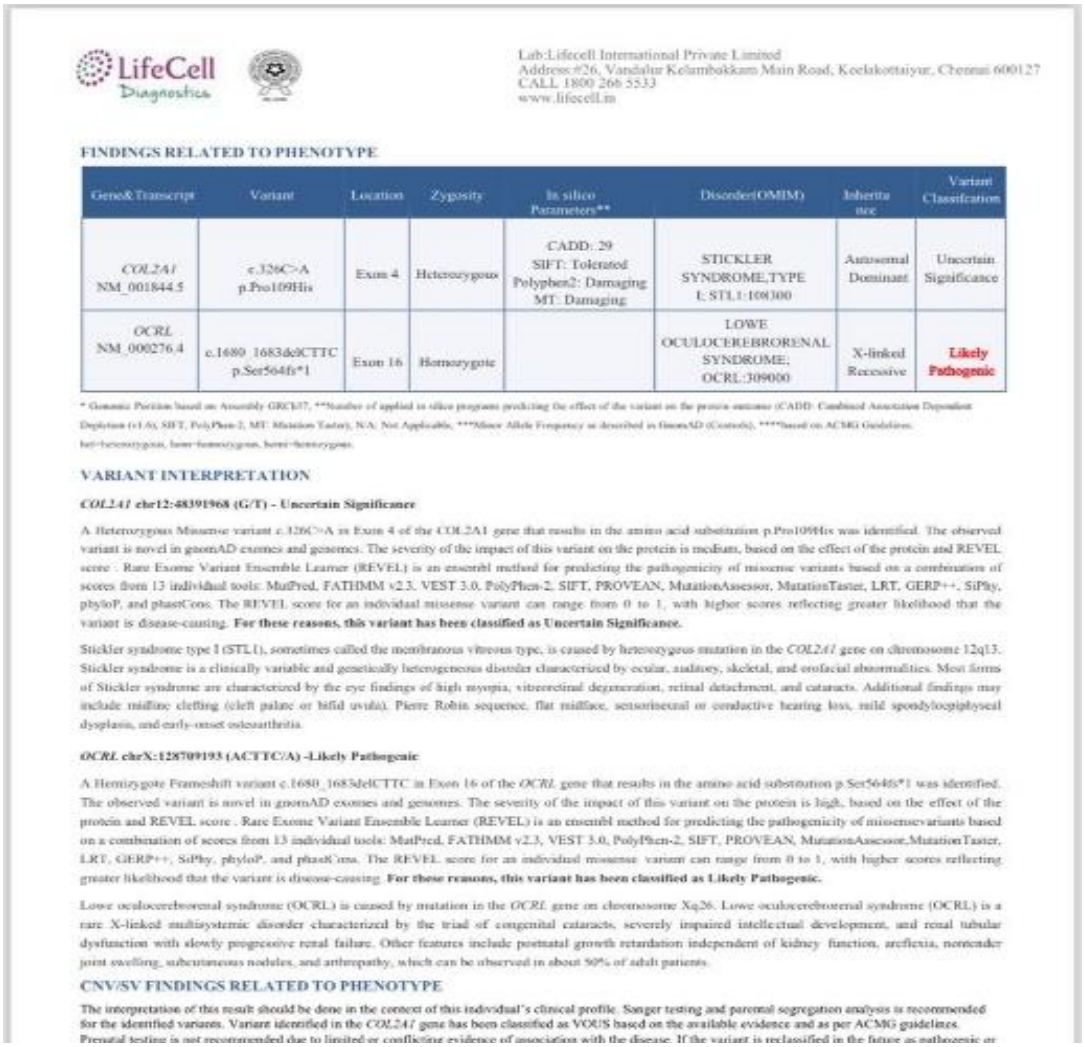


Figure 2: Bilateral congenital cataract



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FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
COL2A1 NM_001844.5	c.326C>A p.Pro109His	Exon 4	Heterozygous	CADD: 29 SIFT: Tolerated Polyphen2: Damaging MT: Damaging	STICKLER SYNDROME,TYPE I; STL1:108300	Autosomal Dominant	Uncertain Significance
OCRL NM_000276.4	c.1680_1683delCTTC p.Ser564fs*1	Exon 16	Hemizygote		LOWE OCULOCEREBRORENAL SYNDROME; OCRL:309000	X-linked Recessive	Likely Pathogenic

* Genomic Position based on Assembly GRCh37, **Number of applied in silico programs predicting the effect of the variant on the protein outcome (CADD: Combined Annotation Dependent Depletion (v1.6), SIFT, PolyPhen-2, MT: Mutation Taster), N/A: Not Applicable, ***Minor Allele Frequency as described in GnomAD (Controls), ****Based on ACMG Guidelines, het=heterozygous, hemi=hemizygous, homo=homozygous.

VARIANT INTERPRETATION

***COL2A1* chr12:48391968 (G/T) – Uncertain Significance**

A Heterozygous Missense variant c.326C>A in Exon 4 of the COL2A1 gene that results in the amino acid substitution p.Pro109His was identified. The observed variant is novel in gnomAD exomes and genomes. The severity of the impact of this variant on the protein is medium, based on the effect of the protein and REVEL score . Rare Exome Variant Ensemble Learner (REVEL) is an ensembl method for predicting the pathogenicity of missense variants based on a combination of scores from 13 individual tools: MutPred, FATHMM v2.3, VEST 3.0, PolyPhen-2, SIFT, PROVEAN, MutationAssessor, MutationTaster, LRT, GERP++, SiPhy, phyloP, and phastCons. The REVEL score for an individual missense variant can range from 0 to 1, with higher scores reflecting greater likelihood that the variant is disease-causing. **For these reasons, this variant has been classified as Uncertain Significance.**

Stickler syndrome type I (STL1), sometimes called the membranous vitreous type, is caused by heterozygous mutation in the *COL2A1* gene on chromosome 12q13. Stickler syndrome is a clinically variable and genetically heterogeneous disorder characterized by ocular, auditory, skeletal, and orofacial abnormalities. Most forms of Stickler syndrome are characterized by the eye findings of high myopia, vitreoretinal degeneration, retinal detachment, and cataracts. Additional findings may include midface clefting (cleft palate or bifid uvula), Pierre Robin sequence, flat midface, sensorineural or conductive hearing loss, mild spondyloepiphyseal dysplasia, and early-onset osteoarthritis.

***OCRL* chrX:128709193 (ACTTC/A) -Likely Pathogenic**

A Hemizygote Frameshift variant c.1680_1683delCTTC in Exon 16 of the *OCRL* gene that results in the amino acid substitution p.Ser564fs*1 was identified. The observed variant is novel in gnomAD exomes and genomes. The severity of the impact of this variant on the protein is high, based on the effect of the protein and REVEL score . Rare Exome Variant Ensemble Learner (REVEL) is an ensembl method for predicting the pathogenicity of missense variants based on a combination of scores from 13 individual tools: MutPred, FATHMM v2.3, VEST 3.0, PolyPhen-2, SIFT, PROVEAN, MutationAssessor,MutationTaster, LRT, GERP++, SiPhy, phyloP, and phastCons. The REVEL score for an individual missense variant can range from 0 to 1, with higher scores reflecting greater likelihood that the variant is disease-causing. **For these reasons, this variant has been classified as Likely Pathogenic.**

Lowe oculocerebrorenal syndrome (OCRL) is caused by mutation in the *OCRL* gene on chromosome Xq26. Lowe oculocerebrorenal syndrome (OCRL) is a rare X-linked multisystemic disorder characterized by the triad of congenital cataracts, severely impaired intellectual development, and renal tubular dysfunction with slowly progressive renal failure. Other features include postnatal growth retardation independent of kidney function, areflexia, nonrender joint swelling, subcutaneous nodules, and arthropathy, which can be observed in about 90% of adult patients.

CNV/SV FINDINGS RELATED TO PHENOTYPE

The interpretation of this result should be done in the context of this individual's clinical profile. Sanger testing and parental segregation analysis is recommended for the identified variants. Variant identified in the *COL2A1* gene has been classified as VOUS based on the available evidence and as per ACMG guidelines. Prenatal testing is not recommended due to limited or conflicting evidence of association with the disease. If the variant is reclassified in the future as pathogenic or

Figure 3: Whole exome sequencing report positive for OCRL gene.

3. Discussion

Lowe syndrome involves the eyes, central nervous system (CNS), and kidneys. All affected boys have dense cataracts and half have glaucoma. Corrected acuity is rarely better than 20/100. Hypotonia is present at birth and the tendon reflexes are usually absent. Hypotonia may improve, but tone never is normal. Motor milestones are achieved slowly and all boys have some degree of intellectual impairment. Proximal renal tubular dysfunction of the Fanconi type is present, including bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, aminoaciduria, low molecular weight proteinuria, sodium and potassium wasting, and polyuria. Slowly progressive chronic renal failure is the rule, resulting in end-stage renal disease after age 10–20 years.

Differential Diagnosis:

1) **Central nervous system**[5]
   - Chromosomal disorders- Prader-Willi syndrome, Trisomy
   - Inborn errors of metabolism
   - Cerebral dysgenesis
   - Spinal cord trauma
2) **Motor neuron**[5]
   - Spinal muscular atrophy
3) **Muscle**[5]
   - Congenital myopathies
   - Metabolic myopathies
   - Congenital muscular dystrophy
   - Congenital myotonic dystrophy
4) **Peroxisomal disorders**[2]
   - Cerebrohepatorenal syndrome (Zellweger syndrome)
   - Neonatal adrenoleukodystrophy
5) **Other genetic defects**[2]
   - Familial dysautonomia
   - Oculocerebrorenal syndrome (Lowe syndrome)
6) **Other metabolic defects**[2]
   - Acid maltase deficiencya
   - Infantile GM1 gangliosidosis

Management-

Symptomatic treatment includes early removal of cataracts, nasogastric tube feedings or feeding gastrostomy to achieve appropriate nutrition, occupational or speech therapy to address feeding problems, standard measures for gastroesophageal reflux, and programs to pro- mote optimal psychomotor development[2].

4. Conclusion

Patients with low syndrome typically presents in infancy with cataracts, progressive growth failure, hypotonia, and fanconi syndrome. Significant low-molecular-weight proteinuria is common. Blindness and renal insufficiency often develop. Characteristic behavioural abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviours), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

Consent

Written informed consent was obtained from the patient's father for publication of this case report.

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