Lowe's (oculo-cerebro-renal) syndrome

Synonyms: oculocerebrorenal syndrome, OCRL, Lowe-Terrey-MacLachlan syndrome and 4,5-bisphosphate 5-phosphatase deficiency

What is Lowe's syndrome?[1]

The syndrome was first described by Lowe, Terrey and MacLachlan in 1952. It is an X-linked condition due to a mutation on the Xq26.1 gene. The mutation of the OCRL1 gene also causes Dent's disease. The classical diagnostic triad includes:

- Congenital cataracts.
- Neonatal or infantile hypotonia with subsequent mental impairment.
- Renal tubular dysfunction progressing to chronic renal failure.

There is a disease spectrum spanning from an isolated tubulopathy (Dent-2 disease) to the most severe presentation of the oculocerebrorenal syndrome described by Lowe et al. in the 1950s.[2]

How common is Lowe's syndrome? (Epidemiology)

It is a rare condition that usually affects just males, with female carriers. There are three recorded cases of the disease affecting females. This might be due to mutation on an autosome rather than the X chromosome or it may represent "infelicitous lyonization in heterozygous females". This relates to the Lyon hypothesis that in females, one of the X chromosomes is suppressed.

The incidence is about 1 in 500,000.[3]

Lowe's syndrome symptoms (presentation) [4]

Lowe syndrome (oculocerebrorenal syndrome) is characterised by involvement of the eyes, central nervous system, and kidneys:

- Dense congenital cataracts are found in all affected boys and infantile glaucoma in approximately 50%. All boys have impaired vision, and corrected acuity is rarely better than 20/100.
- Generalised hypotonia is noted at birth. Deep tendon reflexes are usually absent. Hypotonia may slowly improve with age, but normal motor tone and strength are never achieved. Motor milestones are delayed.
- Almost all affected males have some degree of intellectual disability. 10%-25% function in the low-normal or borderline range, approximately 25% in the mild-to-moderate range, and 50%-65% in the severe-to-profound range of intellectual disability.
- Affected males have varying degrees of proximal renal tubular dysfunction of the Fanconi type, including low molecular-weight (LMW) proteinuria, aminoaciduria, bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, hypercalciuria, sodium and potassium wasting, and polyuria. The features of symptomatic Fanconi syndrome do not usually become apparent until after the first few months of life, except for LMW proteinuria. Glomerulosclerosis associated with chronic tubular injury usually results in slowly progressive chronic kidney disease and end-stage renal disease between the second and fourth decades of life. See also Renal Fanconi Syndrome.

Investigations

The diagnosis is based on typical clinical and laboratory findings and a hemizygous pathogenic variant in OCRL identified by molecular genetic testing. [4]

Urinalysis

Urine will show excessive loss of bicarbonate, with a pH of 6.0 to 7.5. Aminoaciduria, phosphaturia, calciuria, and proteinuria are present. Water resorption is impaired resulting in high volume and low osmolality. There is hypercalciuria and hyperphosphaturia and L-carnitine is lost in the urine.

Blood tests

- Hypokalaemia is unusual.
- Plasma alkaline phosphatase, calcium and phosphorus should be estimated. A rise in alkaline phosphatase is usually the first biochemical indicator of rickets. Carnitine may also be low.
- As the years go by, plasma creatinine will rise and creatinine clearance will fall as chronic renal failure develops.
- Serum glutamic-oxaloacetic transaminase (SGOT), LDH, and CK levels often are elevated.
- There is an elevated concentration of phosphatidylinositol 4,5-bisphosphate, the substrate for the OCRL1 protein and a reproducible cellular abnormality of the actin cytoskeleton in fibroblasts from patients with Lowe's syndrome. There is also an abnormal distribution of gelsolin and alpha-actinin, actin-binding proteins regulated by both phosphatidylinositol 4,5-bisphosphate and calcium that would be expected to be altered in Lowe cells.
- Arterial blood gases will show a metabolic acidosis.

Imaging

- X-ray of the wrists may show the typical changes of rickets.
- MRI scan of the brain may show white matter abnormalities, particularly in the periventricular area. These abnormalities are caused by fluid-filled cysts, which appear to have no clinical significance.

Lowe's syndrome treatment and management[4]

Both surgical and medical interventions are required but there is no cure. Management includes:

- Tube feedings may be needed to treat infant feeding problems associated with hypotonia.
- Early removal of cataracts with postoperative glasses, management of glaucoma.

- Preschool intervention program and individualised education program throughout schooling.
- Behaviour modification plan.
- Anticonvulsant therapy if seizures are present.
- Treatment of renal tubular dysfunction includes:
    - Oral supplements of sodium and potassium bicarbonate or citrate to correct acidosis and hypokalaemia.
    - Oral phosphate and oral calcitriol (1,25-dihydroxyvitamin D3) to correct hypophosphataemia and renal rickets.
    - Treatment of end-stage renal disease with dialysis and renal transplant.
- Human growth hormone therapy to improve growth velocity.
- Treatment for gastro-oesophageal reflux if present.
- Bracing or surgery for severe or progressive scoliosis or joint hypermobility.
- Physiotherapy.
- Resection of fibromas and cutaneous cysts if painful or impairing function.
- Orchidopexy.

Prognosis

Slowly progressive renal failure is the major cause of death. Fanconi's syndrome of the renal tubule predisposes to dehydration and metabolic imbalance, which can be severe. They have a tendency to develop pneumonia due to hypotonia and poor cough reflex. Other causes of death include infection and status epilepticus, and sudden unexplained death can occur. Death usually occurs in the second or third decade of life.

Genetic counselling[4]

Lowe's syndrome is inherited in an X-linked manner. De novo pathogenic variants have been reported in 32% of males affected with Lowe's syndrome. A high risk of germline mosaicism (4.5%) has been identified.

When a mother is heterozygous, each pregnancy has a 25% chance of an affected son, a 25% chance of a heterozygous daughter, a 25% chance of an unaffected son, and a 25% chance of a daughter who is not heterozygous. No affected male is known to have reproduced.

Approximately 95% of heterozygous females older than age 15 years have characteristic findings in the lens of the eye on slit lamp examination by an experienced ophthalmologist using both direct and retroillumination. Once the OCRL pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Further reading

- Murdock N, Chou E; Oculocerebrorenal Syndrome. StatPearls, Jan 2023.
- Ma X, Ning K, Jabbehdari S, et al; Oculocerebrorenal syndrome of Lowe: Survey of ophthalmic presentations and management. Eur J Ophthalmol. 2020 Sep;30(5):966-973. doi: 10.1177/1120672120920544. Epub 2020 Apr 27.

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