Lowe's (Oculo-Cerebro-Renal) Syndrome

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

The syndrome was first described by Lowe, Terrey and MacLachlan in 1952.\(^1\) It is an X-linked condition due to a mutation on the Xq26.1 gene.\(^2\) 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

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.\(^3\)

Presentation

Ocular features

- Hydrophthalmia (congenital glaucoma)
- Cataract

Glaucoma occurs in about half but cataracts are almost invariably present at birth.

Neurological features

- Hyporeflexia and hypotonia are usual features. 'Ragged red fibre' muscle pathology has been described.
- Mean IQ is in the moderate mental handicap range of 40 to 54, with 25% of tested individuals in the normal range of IQ = 70 or more. This should be satisfactory for normal schooling. However, more than 80% have maladaptive behaviours, particularly stubbornness, temper tantrums, and stereotypical behaviours that interfere with mainstream education.\(^4\) They may seem sociable otherwise. Self-injury is not uncommon.
- Seizures occur in about half and typically appear before six years of age. A wide variability in seizure types exists, including myoclonic seizures, generalised tonic-clonic seizures, infantile spasms, and partial complex seizures. The risk of febrile convulsions is 9%, compared with 3% for the general population. See separate article Epilepsy in Children and Young People.

Renal features

Renal dysfunction is characterised by proteinuria, generalised amino aciduria, carnitine wasting, and phosphaturia in the first year of life.

- Renal function is normal at birth but is abnormal by the first birthday. Most patients require alkalinisation therapy and many benefit from supplemental potassium, phosphate, calcium and carnitine.
- Urinary wasting of individual amino acids is milder than in cystinosis. Serum creatinine levels rise with age, heralding inevitable chronic renal failure.\(^5\)
- Hypophosphataemia, metabolic acidosis and hypotonia predispose to rickets and osteomalacia. Despite maintenance of normal serum phosphate levels with therapy, osteopenia is a consistent finding. Fractures are common, especially when learning to walk. The femur is often involved. Scoliosis is common and may progress after puberty. Hypotonia can lead to joint hypermobility. Decreased movements can cause joint contractures. Linear growth decreases after one year of age and bone age lies between the chronologic age and height age.\(^6\)
- The blood concentrations of the muscle enzymes creatine kinase (CK), aspartate aminotransferase and lactate dehydrogenase (LDH) are elevated, suggesting muscle involvement. Total plasma protein, alpha-2-globulin and high-density lipoprotein cholesterol are also raised.

Other common features

- Between 15 and 40% have cryptorchism. Sexual development is normal.
Joint swelling, arthritis, and tenosynovitis are common, especially in the late teens and early adulthood.

**Investigations**

**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.

**Female carriers**
Examination for the carrier state in females has high specificity and sensitivity.

In a trial there were 31 females from three families, known to be either carriers or not carriers by direct DNA analysis. Slit-lamp biomicroscopy, after dilatation of the pupil, was performed by a single observer who was unaware of the subject's status. Carrier women had small, irregularly-shaped, off-white, nonrefractile, radially arrayed, peripheral cortical lens opacities. No false-positives were found among the 31 females examined. Only one false-negative was found in a girl aged five years.

They concluded that slit-lamp examination is a highly accurate and sensitive test for carrier detection in Lowe's syndrome, particularly in women of reproductive age.[6]

**Antenatal diagnosis**
Because of the allelic heterogeneity of the OCRL gene, prenatal diagnosis by molecular analysis is limited to families in which the mutation is already known or in which linkage is informative. A more generally applicable diagnostic test based on biochemical testing is reported for prenatal diagnosis of Lowe's syndrome by measuring phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity in cultured amniocytes.[7]

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

**Ophthalmic surgery**
- Early removal of cataracts, even within the first weeks of life, provides the optimal visual stimulation to the developing brain. Lens implantation is not recommended because of growth of the infant eye and because of the propensity to develop glaucoma.
- Glaucoma develops in about half and is difficult to treat. Surgical implantation of artificial valves to control the release of intraocular fluid is often required.
- Corneal keloids may require surgical removal of the scar tissue, or radiation therapy. Corneal transplantation is difficult because of problems in administering the required intensive postoperative care.
- Sometimes surgical correction of strabismus is required.

**Other surgery**
Orchidopexy may be required.

**Medical management**
- Management of renal tubular acidosis requires careful monitoring of acid base status and electrolytes. Sodium citrate and citric acid or sodium citrate and potassium citrate are required to maintain plasma bicarbonate levels above 20 mmol/L.
- Potassium and calcium supplementation may be needed to offset renal losses.
- Oral carnitine supplementation may be necessary if plasma levels are abnormally low.
Neutral phosphate, vitamin D, and careful maintenance of normal acid-base status are necessary to avoid rickets and osteomalacia.

Other interventions

- There is no clear benefit from special diets.
- Education will need to be adapted according to needs as dictated by both IQ and behavioural problems.
- Hypotonia often causes feeding difficulties. Sucking, swallowing, and chewing may be impaired, and therapy may be helpful.
- Speech and language therapy may be required.
- Physiotherapy may also be beneficial for the many physical problems.

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

If the proband represents a new mutation, the risk to subsequent children is low. If the mother is a carrier, there is a 50% chance of any son being affected and any daughter being a carrier.

Further reading & references

- Lowe Syndrome. Online Mendelian Inheritance in Man (OMIM).

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Document ID: 1013 (v23) Last Checked: 22/03/2010 Next Review: 21/03/2015

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