A case of Lowe syndrome (oculocerebrorenal syndrome): Clinical implications and anaesthetic management

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Introduction

In 1952 Lowe and his colleagues described a syndrome with organic aciduria, decreased renal ammonia production, hydrophthalmos and mental retardation.[1] In 1954, a renal Fanconi syndrome was recognised as being associated with the syndrome,[2] and in 1965 an X-linked pattern of inheritance was determined.[3]

The oculocerebrorenal (Lowe) syndrome is characterised by congenital cataracts, hypotonia, developmental delay, poor growth and renal tubular dysfunction. Clinical problems typically include polyuria, acidosis and hypophosphataemia with rickets and eventually end-stage renal disease.[4] Hypercalciuria and its sequel (nephrocalcinosis and nephrolithiasis), typical of distal renal tubular acidosis, have not been described as cardinal features of the untreated disorder although they reportedly complicate vitamin D and calcium therapy of rickets.[4]

The disease is caused by the mutations of the OCRL gene which is localised at chromosome Xq24-26, coding for enzyme phosphatidyl inositol (4, 5) biphosphatase (Ptdlns (4, 5) P2 phosphatase), responsible for transport of vesicles in the Golgi apparatus.[5] Accumulation of phosphatidyl inositol (4, 5) biphosphate the main substrate for this enzyme in Lowe cells, and mutual disequilibrium of phosphoinositides cause the clinical picture at birth and possibly the later complications.[6]

We report here the perioperative management of a child with Lowe syndrome who was operated for congenital cataract.

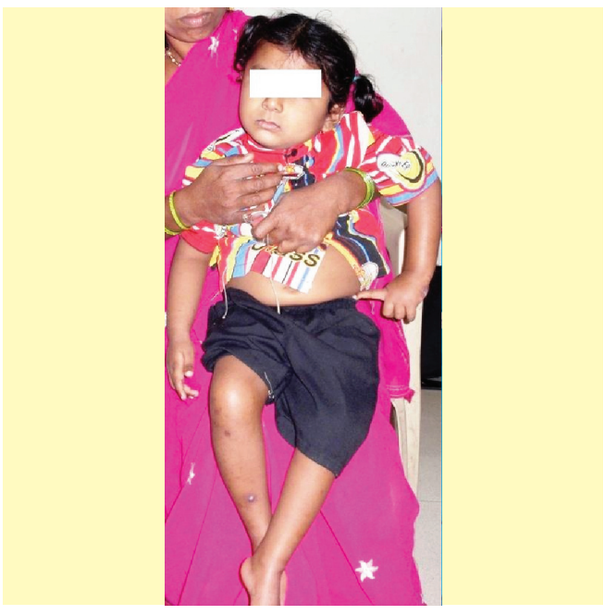
Case description

A three year old child diagnosed with Lowe syndrome was scheduled for bilateral cataract extraction. He presented as underweight, had delayed motor and mental milestones and was hypotonic. He was the fifth born child to a non-consanguineous couple. His parents had already lost two children, both males, at the age of eleven and two months respectively, and both the children had hypotonia and cataracts.

The child was mentally retarded and his speech was reduced to monosyllables. He had no history of seizures.

This child was born out of a normal full term home delivery, and was noticed to have cataract at birth. He had delayed passage of meconium. The parents reported that the child had delayed motor milestones like neck holding and sitting. He used to have frequent respiratory infections. The presence of hypotonia, congenital cataract, metabolic acidosis, and the death of two male siblings who also had hypotonia and cataract led to a high suspicion of Lowe syndrome in this patient. He was treated for acidosis with sodium bicarbonate tablets (soda Mint) in divided doses with frequent blood analysis to maintain serum levels around 20 mmol.l.$^{-1}$

Figure 1: Case of Lowe syndrome



On examination child had microcephaly with frontal bossing, micropthalmos, his posture was limp and floppy and the feel of the muscles was flabby. The child was assigned a mental age of six months.

His body weight was 10 kg (below the third percentile) and head circumference was 45 cm (below the third percentile). There were no involuntary movements, the deep tendon reflexes were sluggish and plantars were flexors. Pulse rate, blood pressure, respiratory and cardiovascular examination were within normal limits.

All routine investigations (haemoglobin, random blood sugar, renal function tests and chest x-ray) were unremarkable. Renal ultrasound did not show any evidence of nephrocalcinosis or nephrolithiasis.

A thyroid function test was also advised to rule out congenital hypothyroidism as the child had delayed passage of meconium, complaints of constipation, delayed milestones, and mental retardation. T3, T4 and TSH values were within normal limits. Although alkaline phosphatase is usually elevated in Lowe syndrome (due to rickets resulting from the urinary loss of phosphates), it was within normal limits in this case.

The child was kept starving for six hours prior to surgery and was started on lactated Ringer's solution 40 ml per hour to prevent dehydration. He was kept warm as hypothermia could worsen acidosis. No premedication was given. General anaesthesia was planned. He was induced with thiopentone sodium 5 mg. kg^{-1}. The trachea was intubated with uncuffed 4.5 sized tracheal tube facilitated by atracurium besylate 0.5 $mg.^{-1}$. Anaesthesia was maintained with 50% each of O_2-N_2O, intermittent halothane (0.2–1%) with incremental doses of atracurium. Pain relief was achieved with fentanyl 2 $mcg.kg^{-1}$. Intraoperative blood sugar and arterial blood gas analysis were done which were again unremarkable.

After the surgery, once spontaneous breathing returned, anaesthesia was reversed with neostigmine 0.05 mg.kg -1 and glycopyrrolate 6 µg.kg -1. Extubation was performed after confirming return of adequate motor power. He was observed in the PACU for 2 h before being transferred to the ward.

Discussion

Lowe syndrome is an uncommon, pan-ethnic disorder with the prevalence of only a few individuals per 100 000 births.[7] It has a recessive X-linked pattern of inheritance which typically affects male children, females acting as carriers. Penetrance is complete,with similar phenotype in the affected males within a given family. The diagnosis is established in affected individuals by demonstrating reduced (< 10% of normal) activity of inositol polyphosphate 5-phosphatase OCRL-1 in cultured skin fibroblasts.[8]

Congenital cataract can be a part of congenital syndromes, due to chromosomal anomalies, systemic associations or prenatal infections. A few are listed in Table I.

At birth, ocular involvement with bilateral cataract and hypotonia may be found in generalised congenital infections (rubella), peroxisomal disorders (Zell Eger syndrome spectrum), Nance-Horan syndrome, congenital myotonic dystrophy type 1, mitochondrial disorders and cystinosis.[3,8]

Although the diagnosis of Lowe syndrome is not straightforward, virtually all patients have some degree of hypotonia with absent tendon reflexes and cataract at birth.

Table I: Congenital syndromes associated with metabolic diseases and prenatal infections

1 Systemic associations	Galactosaemia, galactokinase deficiency, hypoparathyroidism, pseudohypoparathyroidism, mannosidosis, cystinosis, peroxismal disorders, mitochondrial disorders, Smith-Lemli-Optiz syndrome and Lowe syndrome
2 Prenatal infections	Congenital rubella, toxoplasmosis, cytomegalovirus, herpes simplex and varicella
3 Chromosomal abnormalities	Downs, Patau and Edward syndrome
4 Skeletal abnormalities	Hallermann-Streiff-Francois syndrome and Nance-Horan syndrome

Congenital cataract may be associated with another paediatric condition, galactosaemia. This is an X-linked recessive disorder, associated with deficiency of galactokinase enzyme. The infants have problems of failure to thrive, aminoaciduria and mental retardation, in addition to cataract. This child was initially treated as a case of galactosaemia for the first few months of life before the diagnosis of Lowe syndrome was made. Hypotonia and metabolic acidosis due to proximal tubular dysfunction differentiate this condition from galactosaemia.

Thyroid function tests were done to rule out hypothyroidism as the child was mentally retarded, had delayed milestones and complaints of chronic constipation. The results showed normal T3, T4 and TSH levels.

Early diagnosis of Lowe syndrome can be difficult. Low molecular weight (LMW) proteinuria, characterised by the excretion of proteins such as retinol binding protein (RBP) and the lysosomal enzyme N-acetyl -glucosamidinase (NAG), are significantly raised in boys with Lowe syndrome. LMW proteinuria can be seen early in life even in the absence of clinically significant aminoaciduria or other renal abnormalities. Thus, LMW proteinuria may be the most sensitive marker of renal dysfunction that occurs in this disorder.[9]

Hypotonia in these children often causes feeding difficulties. Sucking and swallowing may be impaired in the neonate making them susceptible for aspiration. These children are more susceptible for developing pneumonia because of their hypotonia causing inability to cough effectively. A high incidence of gastro-oesophageal reflux is also noticed. Although tone improves with age, patients never achieve normal muscle tone, and consequently develop problems like hernia and scoliosis.

The renal component of Lowe syndrome comprises type 2 renal tubular acidosis (RTA) (Renal Fanconi syndrome), where the main problem is greatly impaired reabsorption of bicarbonate in the proximal tubule. This results in urinary loss of HCO_3^- with inappropriately high urine pH. The bicarbonate is replaced by chloride in the circulation resulting in hyperchloraemic acidosis.[10] The increased distal Na^+ delivery results in hyperaldosteronism with consequent potassium wasting.

Although hypercalciuria and nephrocalcinosis typical of Type 1 RTA (distal RTA) are not cardinal features of Lowe syndrome, isolated cases are reported in literature. This picture can be complicated in these children as they are put on calcium and vitamin D therapy making them more susceptible for stone formation. Renal tubular functions may be normal a birth but typical abnormalities are often detected by first decade of life.

Glomerular function falls slowly with age, with renal failure predicted between the second and fourth decade of life.

Serum creatinine levels remain normal during the first decade of life. As creatinine is made in muscles, the blood levels of creatinine lower than expected for a given degree of renal failure may be observed as the muscle mass is reduced. A 24 hour urine creatinine or creatinine clearance gives a more accurate estimate of kidney functions.

As the kidneys are not able to conserve water and concentrate urine normally, strict perioperative precautions to prevent dehydration should be taken. Hypothermia can cause disturbance in peripheral circulation and worsen metabolic acidosis, so strict temperature monitoring is advised.[11]

The most important problem affecting anaesthetic management is chronic metabolic acidosis. Any agent that rapidly decreases the sympathetic tone, in the presence of acidosis may potentiate circulatory depression. Since most opioids are weak bases, acidosis can increase the fraction of the drug in the non ionised form and facilitate penetration of the opioid into the brain, causing increased sedation and respiratory depression.[12]

As these children are already hypotonic, any degree of hypokalaemia increases muscle weakness. It is recommended to use short acting muscle relaxants like atracurium with nerve stimulators to follow up the degree of paralysis and adequacy of reversal. A careful watch on K+ levels is recommended as serious cardiac arrhythmias can occur with hypokalaemia.[12]

Although there is albumin loss in urine, it is usually not severe enough to cause nephrotic syndrome. A generalised aminoaciduria also usually does not cause any clinical problem, although it helps in establishing the diagnosis.

Loss of L-carnitine is associated with a decreased ability to tolerate fasting, hepatomegaly and low blood sugar. Strict monitoring of blood sugar is mandatory as hyperglycaemia and secondary insulin secretion may further lower serum potassium.[12]

A high arched palate, small mouth, crowding and poor alignment of teeth secondary to rickets make intubations difficult in these cases.

Boys with Lowe syndrome are generally of normal length at birth, but by one year of age most usually fall below the normal range.[3] These children are prone to vitamin D deficiency (rickets) as dihydrocholecalciferol of (vitamin D) is made in renal tubules, leading to a higher incidence of fractures. Rickets can be improved by giving preparations of neutral phosphate or vitamin D preparation like calcitriol.

The nervous system involvement causes problems including hypotonia, intellectual impairment and behavioural problems like tantrums, stubbornness, stereotypy and obsessions. Many children need long term anticonvulsants for seizure disorders. Cranial MRI may show ventriculomegaly and cysts in the periventricular regions.

Lowe syndrome is one of the rare conditions were congenital cataract and glaucoma may co-exist. Corneal degeneration resulting in keloid formation can cause visual impairment later in life. As many of these children have coexisting glaucoma it is preferable to use non-depolarising muscle relaxants for intubation as the use of the muscle relaxant succinylcholine can increase the intraocular pressure. Implantation of an artificial lens is also not recommended because of the propensity to develop glaucoma. Direct pressure on the eye from a tightly fitting mask and poor prone position must be avoided as these can again increase intraocular tension.[12]

Treatment is usually supportive like cataract extraction, speech therapy, anticonvulsants and management of renal complications.[3] Bicarbonate therapy is used at the dose of 2–3 mmol.kg-1 per day every six to eight hours to maintain serum levels around 20 mmol.l-1. The other drugs recommended are sodium or potassium phosphates for correcting phosphate depletion and Vitamin D to prevent rickets.
These children can come to the operating room for congenital cataract, glaucoma repair, corneal keloid excision and removal of corneal cysts at a very early age. Surgical correction of undescended testis, hernia repair, fractures, correction of scoliosis and renal transplantation are the other surgeries usually performed in them.

Metabolic acidosis and hypokalaemia are the important aspects to be noted and should be appropriately corrected during emergency situations. Preoperative ECG is necessary to show cardiac arrhythmias caused by hypokalaemia.[12]

The diagnostic triad of the oculocerebrorenal syndrome of Lowe includes congenital cataract, neonatal or infantile hypotonia with subsequent mental impairment, and renal tubular defects. Activity of the enzyme phospatydyl inositol (4, 5) biphosphatase can be measured in cultured skin fibroblasts to confirm the diagnosis in affected males.[2]

Molecular genetic testing by sequence analysis of the OCRL gene identifies mutations in approximately 95% of males with Lowe syndrome. Fish analysis can detect gene deletions.[8]

Slit lamp examination is a highly accurate and sensitive test for carrier detection.[13] The typical findings are lenticular opacities or a single dense posterior cataract.

Prenatal diagnosis of at-risk pregnancies is done using molecular analysis of phospatidyl inositol triphosphatase (Ptdlns (4, 5) P2 phosphatase) in cultured chorionic villi.

The uneventful course of anaesthesia was related to thorough systemic evaluation and careful anaesthetic management.

Conflict of interest: None

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