

Low Syndrome (Oculocerebrorenal Syndrome of Lowe): A Case Report of Two Brothers from India

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ABSTRACT Lowe syndrome (oculo-cerebro-renal syndrome of Lowe) is a rare X-linked recessive disorder characterized by the involvement of eyes, brain and kidneys. It is caused by the deficiency of enzyme phosphatidylinositol 4, 5-bisphosphate 5-phosphatase, which is required for the intracellular trafficking, second messengers and for the other aspects of cellular metabolism. The gene coding for this enzyme, OCRL1, has been localised at Xq25-q26.1 and mutations in it are reported to cause Lowe Syndrome. In this article we report two male siblings, from North India, with Lowe syndrome.

INTRODUCTION

Lowe syndrome is also known as Oculocerebrorenal syndrome of Lowe (OCRL) or Lowe-Terrey-MacLachlan syndrome. It is a rare, multisystem, X-linked recessive disorder (Streiff et al. 1958) that was first reported by Lowe, Terry and MacLachlan in 1952. It is characterised by the presence of developmental abnormalities involving eyes, brain and kidneys (Lowe et al. 1952). Lowe syndrome is clinically suspected in those males who show the typical phenotype that includes deep set small eyes, frontal bossing, elongated face, bilateral dense congenital cataracts, infantile congenital hypotonia, delayed development, and proximal renal tubular dysfunction of the Fanconi type. Infantile glaucoma, seizures, behaviour problems, language inability, absent deep tendon reflexes, and short stature are also frequently noted in these cases. Most of the Lowe syndrome patients love music and rhythm

(Wappner 2001). It has been suggested that Lowe syndrome should be considered in boys with cataracts and glomerular disease, even in the absence of renal tubular defects and frank mental retardation as a wide range in the severity of the features has been reported among cases of Lowe syndrome (Gropman et al. 2000; Nussbaum and Suchy 2001). Most of the Lowe syndrome patients die in 2nd or 3rd decade of their life and the death is usually due to progressive renal failure. Death from dehydration, pneumonia, and infections has been reported to occur in all age groups (McSpadden 2000).

Lowe syndrome (OCRL) is reported to have a prevalence of only a few cases per 100,000 births (Wappner 2001). The incidence and prevalence of this syndrome in India is not known. Being an X-linked recessive disorder, usually only males are affected, however, a few female cases of Lowe syndrome have also been reported, who either are due to lyonization in the heterozygous females (Svorc et al. 1967) or have X; autosome translocation involving the OCRL1 locus resulting in OCRL phenotype (Hodgson et al. 1986; Mueller et al. 1991).

The X-linked inheritance in Lowe syndrome was first suggested by Streiff et al. (1958). Hodgson et al. (1986), on basis of their studies of a balanced X; autosome translocation, were the first to suggest that the Lowe syndrome locus is in band Xq25. The close linkage of the OCRL to the RFLPs mapping to Xq24-26 was reported by Silver et al. (1987). Wadelius et al. (1989) observed that DXS42 marker was the most closely linked marker. Its final chromosomal localization is Xq25-q26.1 (OMIM 2002; Table 1). Lowe syndrome or OCRL is caused by mutations in the gene OCRL1 (Nussbaum and Suchy 2001). Lin et al. (1997) reported 11 different

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Table 1: The basic genetic information about Lowe syndrome

Disease phenotype	Lowe syndrome
Inheritance pattern	X-linked recessive
Cytogenetic location	Xq25-q26.1
MIM number	309000
HUGO/GDB nomenclature (Approved gene symbol)	OCRL
Alias gene symbol	LOCR, OCRL1, INPP
Approved gene name	Oculocerebrorenal syndrome of Lowe
Protein	Inositol polyphosphate 5-phosphatase OCRL-1
Total number of exons	23
Total number of nucleotides	4935
GDB ID	119461
Locus Link ID	4952
Mouse homologue	Ocr1

mutations in OCRL gene in 12 unrelated patients with OCRL; while Satre et al. (1999) reported 7 new mutations in 8 unrelated patients of OCRL and identified 2 new microsatellite markers for the OCRL1 locus. Germline mosaicism for OCRL has also been reported (Satre et al. 1999; Monnier et al. 2000). Till now 79 mutations have been reported for the OCRL1 gene (LSMD 2002).

The main pathophysiological defect in the Lowe syndrome is marked reduction of the OCRL1 protein (phosphatidylinositol 4,5-bisphosphate 5-phosphatase) (Suchy et al. 1995; Zang et al. 1995) caused by the mutations in the OCRL1 gene. This enzyme, a 105 kDa protein, is present in the trans Golgi apparatus (Dressman et al. 2000) and plays a crucial role in the cellular trafficking, second messengers and other aspects of cellular metabolism. The deficiency of this enzyme affects the intracellular protein sorting especially within the polarized cells like renal epithelium and the lens. It may be the cause of associated epithelial cell phenotype i.e., congenital cataract and renal tubular dysfunction seen in the patients of OCRL (Erneux et al. 1998).

CASE REPORT

Two brothers, aged 7 years and 4.5 years, were referred to the Centre for Genetic Disorders with complaints of delayed mental and motor milestones, decreased vision and involuntary purposeless movements of hands and feet. Both the children were born via lower cervical caesarean section undertaken due to fetal

distress. The children were born out of a non-consanguineous marriage and the detailed pedigree analysis did not reveal any positive family history. The mother had one spontaneous abortion at 1.5 months of pregnancy between the affected sibs due to excessive bleeding. The youngest sister in the sibship was normal.

The physical examination of the 4.5-year old child revealed flat occiput, frontal bossing, parietal prominence, high arched palate, bilateral congenital cataract with mongoloid slant to eyes, prominent costochondral junctions, decreased visual acuity, nystagmus, cryptochoid testes, scoliosis, short stature (proportionate), severe hypotonia, hyporeflexia and joint hypermobility (Fig. 1 and 2). As infant he could hear and speak a few words but could not stand by himself and had fractures of legs without any history of trauma. He had persistent ear discharge which recurred when the antibiotics were stopped. There was a history of weight loss during infancy, and chronic constipation since birth.

The clinical features of the 7-year old sib resembled those of the younger sibling. In addition he showed genu valgum (bowing of legs), speech limited to cries only, cryptochoid testes, nystagmus, cheilosis at the angle of mouth, anaemia and malformed teeth. This child also had bilateral cataract for which he had been operated at the age of 4 years. As infant he could hear and developed some speech at 1.5 years, but it was lost by the age of 2 years. He started to walk at 2 years of age and then stopped it at 3 years of age. His legs got bowed under strain from heavy upper body (Fig. 3). Both the patients had no appreciable appetite.

The routine clinical laboratory examination of both the sibs showed dilute urine, aminoaciduria, proteinuria and metabolic acidosis. Low levels of serum sodium and potassium, but elevated chloride levels were noted. The radiological evidence of rickets was present in both the children (Fig. 4). Both the patients and their mother were found to have normal chromosomal constitution.

DISCUSSION

Lowe syndrome, first described by Lowe and his associate in 1952, is an X-linked multisystem disease. Few female cases have been reported who have different genetic mechanism of disease usually X; autosome translocations. The



Fig. 1. Hyper-mobility at the hip joint in older sib.



Fig. 2. Presence of frontal bossing and deep set eyes in younger sib.

typical facial features in Lowe syndrome that include deep set small eyes, frontal bossing and elongated face (Lowe et al. 1952) were present in our cases who also showed flat occiput, parietal prominence and mongoloid slant to eyes. Both of our patients were short in height as compared to the individuals of their age. The length of



Fig. 3. Scoliosis and bending of legs in younger sib.

Lowe syndrome patients at birth is usually normal; however, by the end of first year, the short stature due to below normal linear growth becomes evident. The presence of chronic renal disease and acidosis along with rickets also contributes to the short stature. The average height of the adults is about 5' (153 cms) but the adult head circumference and the sexual development are usually normal (McSpadden 2000).

Athreya et al. (1983) and Elliman and Woodley (1983) observed that teenagers and adults with Lowe syndrome, often show swelling of joints, arthritis, tenosynovitis, and subcutaneous benign fibromas, often on the hands and feet and most especially in areas of repeated trauma. Superficial cysts may occur at multiple sites including the mouth, teeth (blue dome cysts), buttocks, and lower back. These can be painful and may become superinfected (McSpadden 2000; Nussbaum and Suchy 2001).

Both of our cases showed scoliosis, hypotonia and hypermobility of joints. The



Fig. 4. X-ray showing signs of rickets in younger sib.

younger patient had history of constipation since birth. He was unable to stand, while the elder brother had started to walk and then stopped at the age of 3 years. Similar observations have also been made by McSpadden (2000) who reported that scoliosis occurs in approximately 50% of the Lowe syndrome cases due to decreased truncal tone. Hypotonia in these patients increases the risk for chronic constipation and the development of hernias, especially inguinal. Hypermobility joints may result in joint dislocation, especially of the hips and knees. Decreased muscle tone may result in delayed motor milestones, and some patients may never walk and need wheelchair for mobility. Cryptorchidism, as seen in both of our cases, has been reported in 15-40% of boys with Lowe syndrome (McSpadden 2000). In such cases, the onset of puberty may be delayed, but otherwise male secondary sexual development is normal.

Cataract and nystagmus was present in both of our patients. Such ocular anomalies have been observed in Lowe syndrome patients. Cataracts, strabismus, retinal dystrophy, secondary corneal scarring, and calcific band keratopathy with

keloid formation seen in such patients cause visual impairment (Cibis et al. 1982; McSpadden 2000; Nussbaum and Suchy 2001). Glaucoma has also been often reported and infantile glaucoma in them is difficult to control and frequently results in buphthalmos and progressive visual loss (McSpadden 2000; Nussbaum and Suchy 2001).

Intellectual impairment varying from low-normal to severe mental handicap is usually seen in patients with Lowe syndrome (Kenworthy et al. 1993). Amongst our cases the elder sib had started to speak and then lost this ability by 2 years of age, the younger one could still speak a few words. According to McSpadden (2000) the language development is delayed in such patients and they learn to communicate verbally to some extent by age seven years, and a few may eventually become loquacious.

Charnas and Gahl (1991) and Kenworthy et al. (1993) reported that in Lowe syndrome patients, behavioral problems like self-stimulation or stereotypic and obsessive-compulsive behaviour, violent tantrums, irritability, rigidity or aggressive and self-abusive behaviour occur. Both of our patients also showed behavioural disturbances and in them involuntary purposeless movements of hands and feet were observed. Although there was no history of seizures in our patients, about half of the patients of Lowe syndrome are reported to have seizure disorders, which can be generalized type tonic-clonic seizures, myoclonic seizures, infantile spasms or partial-complex seizures and these usually start before six years of age (McSpadden 2000). Febrile seizures also occur in these patients more frequently.

Our cases showed dilute urine, aminoaciduria, proteinuria and metabolic acidosis with low serum sodium and potassium levels but elevated chloride levels. The significant acidosis and hypokalemia is caused due to the loss of bicarbonate, phosphate and sodium (Wappner 2001). The elevated serum concentration of high-density cholesterol, Creatinine Kinase (CK), Aspartate Aminotransferase (AST), and Lactate Dehydrogenase (LDH) are occasionally noted in cases of Lowe syndrome but are of uncertain significance. The alpha-2 globulin level, Thyroxine (T4), Thyroxine-binding Globulin (TBG), and Erythrocyte Sedimentation Rate (ESR) may also be elevated in such patients (McSpadden 2000; Nussbaum and Suchy 2001).

It is the loss of calcium and phosphate in Lowe syndrome patients that results in rickets, osteoporosis, and dental problems as seen in our cases. Wasserstein (2002) also observed that in Lowe syndrome, the radiographs of the wrists show changes typical of rickets, including metaphyseal flaring and osteopenia along with an increased risk for fractures, especially of the femur. MRI of the brain in Lowe's patients may show white matter abnormalities. Particularly in the periventricular area, there are fluid-filled cysts of varying sizes in 30-40% of patients, which appear to have no clinical significance. Cysts are also seen in the kidneys (Charnas and Gahl 1991; Demmer et al. 1992; Carroll et al. 1993; Ono et al. 1996; McSpadden 2000). The typical histological renal findings indicate atrophic tubular epithelial cells and interstitial fibrosis. The tubular lumina may be filled with proteinaceous material (Acker et al. 1967).

MANAGEMENT STRATEGIES AND GENETIC ASPECTS

Lowe syndrome should be differentiated from other disorders associated with congenital cataract, hypotonia, proximal renal dysfunction and developmental delays such as congenital generalized infections, Zellweger syndrome and its variants, Nance-Horn syndrome, Smith-Lemli-Opitz syndrome, congenital myotonic dystrophy, disorders of mitochondrial oxidative-phosphorylation (cystinosis), etc. (Wappner 2001). The Lowe syndrome patients usually do not survive beyond the second or third decade of life. The major cause of mortality is slow and progressive renal failure. The Fanconi-type renal tubular dysfunction predisposes these patients to severe dehydration and metabolic imbalance. These patients also have a tendency to develop pneumonia due to hypotonia and poor cough reflex. The other causes of death include infections and status epilepticus, and in some cases sudden unexplained death can also occur.

There is no specific treatment for Lowe syndrome. It is only symptomatic and requires the consultation of physicians from various fields of medicine. The cataracts should be surgically removed and the corneal and conjunctival keloids should be resected if they obstruct the vision. Strabismus and glaucoma also need surgical intervention.

The seizures in these patients can be controlled through anticonvulsant drugs. The electrolyte replacement should be given orally or intra venously depending upon the need. The improvement in growth occurs with human growth hormones. Usually, the undescended testis descend with time, but in some cases hormone therapy or even surgery may be required. The cysts and fibromas, if painful, can be resected.

The low protein diets have often been recommended for the patients with Lowe syndrome, so as to offset the renal disease but others feel that no clear benefit from such diets has been adequately demonstrated (Wasserstein 2002). Physiotherapy should be considered to avoid the formation of contractures.

CARRIER DETECTION

The females who are carriers of Lowe syndrome are usually normal and asymptomatic. There is relatively high rate (4.5%) of germline mosaicism in the mothers of Lowe syndrome patients (McSpadden 2000), therefore, it is important that the mothers of Lowe syndrome boys and all other at-risk female relatives should be evaluated for carrier status. The risk for the sibs and the subsequent genetic counselling depends upon the carrier status of the mother and the determination of the exact mutation in the proband. Lin et al. (1999) observed that lens opacities seen upon slit-lamp examination in the heterozygotes of OCRL are highly accurate and specific in over 95% of cases and this can be used as a sensitive test for the detection of carriers. These opacities are small, irregularly-shaped, off-white, non-refractile, radially arrayed, involving the peripheral cortical lens. The results from these examinations correlate well with the results of molecular genetic studies in post pubertal carrier females (Richards et al. 1965; Lin et al. 1999; McSpadden 2000; Roschinger et al. 2000; Nussbaum and Suchy 2001).

Precise carrier detection by direct DNA analysis is possible in the families where mutation in the OCRL gene is known. If the affected male is not available, and the diagnosis has been confirmed by enzyme analysis, the molecular genetic testing for carrier detection in high-risk females may be done by denaturing

high performance liquid chromatography (DHPLC) for mutational screening of exons 10-18 and exons 19-23 of the OCRL gene (Lin et al. 2000). However, as only about 93% of mutations are located in these exons, not all carrier females would get detected.

The markers used for studying the Lowe syndrome's linkage to OCRL locus are highly informative and show strong linkage to this locus (Nussbaum et al. 1997). Therefore, linkage analysis can be undertaken for families having more than one affected member or when a known disease-causing mutation can not be identified (Reilly et al. 1988; Wadelius et al. 1989; Lin et al. 1999). Linkage analysis can also be considered in families with only one affected male but, the high rate of germline mosaicism (4.5%) that has been documented in Lowe syndrome can confound the results (Satre et al. 1999; Monnier et al. 2000).

Prenatal testing is possible for at risk pregnancies, either by molecular analysis or by biochemical testing in which the activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase is measured in cultured amniocytes (Suchy et al. 1998).

Till now 79 mutations have been reported for Lowe syndrome (LSMD 2002). There are no reports of any mutation in the Lowe syndrome patients from India. The molecular analysis of our two cases is in progress.

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