Management of Lowe syndrome: a case report

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Lowe syndrome (the oculocerebrorenal syndrome of Lowe, OCRL) is a multisystem disorder characterized by anomalies affecting the eyes, nervous system and kidneys. The disorder was first recognized by Lowe et al. in 1952, and described as a unique syndrome with organic aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation. In 1954, renal Fanconi syndrome was recognized as being associated with Lowe syndrome and in 1965, a recessive X-linked pattern of inheritance was determined. Lowe syndrome is a very rare disease, with an estimated prevalence in the general population of 1 in 500,000. According to the Lowe Syndrome Association (LSA) in the USA, the estimated prevalence is between 1 and 10 affected males in 1,000,000 people, with 190 living in the year 2000. The Italian Association of Lowe Syndrome estimated that there were 34 Lowe syndrome patients (33 boys and one girl) living in Italy in the year 2005. It almost exclusively affects males. Physicians may not be familiar with Lowe syndrome due to its rarity.

The disease is caused by pathogenic DNA variations in the OCRL1 gene on chromosome Xq24-26, which encodes phosphatidyl inositol polyphosphate 5-phosphatase. More than 100 pathogenic DNA variations leading to Lowe syndrome have been described, of which more than 90% are located in two hot spots (exons 10-18 and 19-23) in the OCRL1 gene. The pathogenesis of Lowe syndrome due to deficiency of a phosphatidyl inositol 4,5-bisphosphate 5-phosphatase in the Golgi complex is unknown. Clinical and laboratory studies eventually lead to the correct clinical diagnosis, which can be confirmed by molecular studies of the OCRL1 gene located on chromosome Xq24-26. The diagnostic triad of Lowe syndrome includes eye anomalies (congenital cataracts and infantile glaucoma) resulting in impaired vision, neurological deficits (infantile hypotonia with subsequent mental impairment and the absence of deep tendon reflexes), and renal tubular dysfunction of the Fanconi type with glomerulosclerosis, resulting in progressive chronic renal failure and end-stage renal disease. Cataracts should be removed early in order to avoid amblyopia. Early targeted rehabilitation therapy is necessary to treat hypotonia. Renal tubular acidosis must be recognized and treated promptly with alkali supplements. These supplements should include citrates (sodium and/or potassium citrate) and sodium bicarbonate in various doses and combinations, to maintain serum bicarbonate levels. The longest reported survival was that of a 54-year-old patient. Quality of life depends on the extent of
the mental and renal manifestations. Some patients may enjoy a discrete social life and assisted working capacity. Early diagnosis and treatment of metabolic disturbances may delay morbidity and mortality in this syndrome.

The Case

An 8-year-old boy with aphakia was scheduled for surgical removal of posterior capsule opacification (PCO). In May 2013, he was referred from the Department of Ophthalmology to the Department of Child Health for the management of anemia. He was the only child of non-consanguineous parents. The mother had no history of any illness, and did not take drugs or herbal medications during pregnancy. He was delivered vaginally, cried spontaneously, and had full term gestational age with a birth weight of 3,900 grams. No icterus, dyspnea or cyanosis were noted. He was well until the age of 4 months when white patches in both eyes were noted. He was brought to a local ophthalmologist, then referred to our hospital. He was diagnosed with congenital cataracts, cheloids and nystagmus in both eyes and underwent surgery to remove the cataracts. However, he was not followed up routinely due to parents’ financial difficulties.

The PCO recurred at the age of 5 years, but the parents were only able to bring him to the hospital 2 weeks prior to the referral to our department. The ophthalmologist scheduled another surgery. However, severe anemia was found during the pre-surgical work-up, hence, the patient was transferred to the Department of Child Health at the age of 8 years. At the Pediatric Hematology Ward, the anemia was established to be caused by chronic disease and he received a series of packed red blood cell transfusions. Persistent hypokalemia and hyponatremia were noted and further workup showed that he also had polyuria and polydipsia. His milk feeding was increased to more than 1,500 mL per day. He was subsequently referred to the Pediatric Nephrology Division for further management.

His basic immunizations were complete. His developmental milestones were delayed, as he was unable to sit down or talk at the time of presentation. The family history was unremarkable.

On admission to the Pediatric Nephrology Ward, he was alert, but weak. As his height was 79 cm (less than 3rd centile) and his weight was 9 kg (less than 3rd centile), he was considered to have growth failure (Figure 1). His head circumference was 44 cm (less than -2 SD) (Figure 2), so he was considered to have microcephaly. He looked pale, but was not tachypneic or tachycardic. His blood pressure (BP) was 110/70 mmHg (95th centile BP for his age and height was 111/75 mmHg), respiratory rate 26 x/minute, pulse 110 x/minute and axillary temperature 36.5°C. He had frontal bossing, deep set eyes and chubby cheeks. Caries and poor dentition were also seen. Neuroocular examination revealed nystagmus in both eyes with posterior capsule opacification and cheloids. Chest examination revealed rachitic rosary with Harrison’s groove. His lungs were clear. The abdomen was flat and no organomegaly was palpated. Bilateral pedal edema was not noted. Neurological examination showed hypotonia, floppy limbs, drop foot, and areflexia, with a 360 degree range of move-
movement in all extremities with athetoid involuntary movements seen occasionally. His urine output was 9-10 mL/kg/hour.

Laboratory studies during his hospitalization revealed anemia with hemoglobin level of 5.05 g/dL, hematocrit 17%, leukocyte count 6,800/µL, platelet count 147,000/µL. Serum electrolyte measurements revealed hypokalemia, hyponatremia, and hypophosphatemia with sodium level 118 mmol/L, potassium 2.2 mmol/L, calcium 8.4 mg/dL, chloride 100 mmol/L and phosphate 2.3 mg/dL. Repeated hyponatremia and hypokalemia findings occurred during hospitalization. Serum alkaline phosphatase and aspartate aminotransferase were increased, at 189 g/dL and 87 IU/L, respectively. There was proteinuria and blood gas analysis revealed metabolic acidosis with bicarbonate level of 13 mmol/L. The glomerular filtration rate (GFR 58 ml/minute/1.73m²) was decreased, with urea level 25 mg/dL and creatinine 0.7 mg/dL. From all data, we suspected that the patient suffered from Fanconi syndrome that needed further work up. There were no evidence of toxoplasma or rubella virus infections, as IgM and IgG levels for toxoplasma and rubella were negative. He also had normal thyroid function tests.

Chest X-ray revealed widened bilateral anterior costae with coarse bone trabeculation that could have been caused by anemia or rickets (Figure 3). His bone age was delayed, with features that seemed to be appropriate for a 6-month-old boy (Figure 4). The right kidney size was 9.26 cm and the left kidney was 8.99 cm. Both kidneys appeared echogenic with
loss of corticomedullary differentiation from renal ultrasound, and assumed to be parenchymal kidney disease (Figure 5). The 2D-echocardiogram revealed no left ventricular hypertrophy, with normal structure and good systolic function [left ventricular ejection fraction (LVEF) 75% and fractional shortening (FS) 42%]. Partial hypogenesis of the corpus callosum was seen from head CT-scan (Figure 6). A bone survey revealed brachiocephaly and decreased skull bone density, bowing of the humerus and ulna bilaterally, widened distal metaphyses of the femur and proximal metaphyses of the tibia bilaterally, as well as generalized osteopenia (including pelvis, thoracolumbar spine, and lower extremities) (Figure 7).

Based on the history, clinical manifestations, laboratory and radiology data, the patient was diagnosed to have Lowe syndrome with stage 3 chronic kidney disease (CKD). Subsequent management included

**Figure 5.** Renal ultrasound: right kidney size 9.26 cm and left kidney 8.99 cm; both kidneys appeared echogenic with loss of corticomedullary differentiation

**Figure 6.** Head CT scan: partial hypogenesis of the corpus callosum
ophthalmic surgery for PCO, physical rehabilitation and proper medications to supplement bicarbonate, salt (sodium and potassium) wasting and vitamin D. Unfortunately, we were unable to check parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D3] levels due to financial constraints. Vitamin D supplementation was not covered by the government and could not be afforded by the parents. The surgery
was cancelled due to his unstable serum electrolyte levels, following discussion of benefits and risks of surgery with the parents. He was then discharged with oral supplementations of bicarbonate and salt.

The patient did not return for routine follow up due to financial constraints. On the last home visit on August 17, 2013, the patient was in stable condition without any medications (Figure 8).

**Discussion**

Based on the history, clinical manifestations and laboratory data, the patient was diagnosed as having Lowe syndrome, with oculocerebrorenal manifestations comprising of congenital cataracts, cheloids and nystagmus (eye manifestations), areflexia, hypotonia of extremities, developmental delay (nervous system manifestations) and kidney manifestations with stage 3 CKD due to Fanconi syndrome [polyuria, proximal renal tubular acidosis, proteinuria, hypokalemia, hypophosphatemia, anemia, growth failure, and rickets (dental caries, delayed bone age, generalized osteopenia, and rachitic rosary)].

Clinical and laboratory studies eventually lead to the correct clinical diagnosis, which can be confirmed by molecular studies of the OCRL1 gene located on chromosome Xq24-26. Pre- and postnatal diagnoses are made by enzymatic and molecular analyses. Antenatal diagnosis is made by enzymatic activity in cultured chorionic villi at 9-11 weeks or in cultured amniotic fluid cells at 15-20 weeks. An early diagnosis based only on clinical criteria can be difficult and may not be confirmed for several years as the clinical features may be nonspecific or absent during the early stages. Facial dysmorphism is often present and consists of frontal bossing, deep-set eyes, chubby cheeks and fair complexion. Dental findings include prolonged retention of primary teeth, chronic subrachitic state, enlarged pulp chambers and mildly dysplastic dentin formation.

Eye, central nervous system and kidney involvements are required for the diagnosis of Lowe syndrome including the following: 1.) Cataracts are a hallmark of Lowe syndrome and are present at birth in all the male patients. Glaucoma (present in 50% of patients) with or without buphthalmos, is detected within the first year of life and sometimes even later. Sight sharpness is compromised by aphakia, and together with retinal dysfunction is responsible for nystagmus. Corneal and conjunctival cheloids (present in 25% of patients) further compromise the sight. Female carriers of OCRL have no clinical symptoms but do show lens abnormalities in the form of tiny punctate opacities in the cortex visible by slit lamp examination; 2.) Central nervous system: a serious or very severe hypotonia is present at birth, often with an absence of the deep tendon reflexes. Motor development is retarded and the autonomous gait becomes apparent generally after the third year. About 10% of patients show slight mental retardation. Mental retardation may be moderate or severe, with an intelligence quotient (IQ) of 50 or less. Approximately 50% of the patients over 18 years of age have seizures, and up to 9% of patients present with febrile convulsions. Cranial magnetic resonance imaging (MRI) may show a light ventriculomegaly and multiple periventricular cystic lesions in a by stander of the patients. No significant nerve and muscle pathologies are present and they are not useful for diagnosis. Neuropathological examination of OCRL brains has been reported to range from completely normal to variously abnormal, with no specific pathologic findings; 3.) Renal disease is primarily characterized by renal Fanconi syndrome. The first symptoms generally develop during the first months of life but the severity and age of onset vary and tend to worsen with age. Symptoms are generally related to renal bicarbonate, salt and water wasting, causing growth failure. Later, generally during the second decade of life, a significant number of patients develop chronic renal failure, which may lead to end-stage renal failure and require dialysis. Symptoms related to the renal Fanconi syndrome include: a.) polyuria, polydipsia, dehydration, recurrent vomiting and growth failure; b.) low molecular weight proteinuria, which appears to be present in all patients and may be helpful for perinatal diagnosis; c.) proximal renal tubular acidosis; d.) renal phosphate wasting, leading to the development of renal rickets, osteomalacia, and pathological fractures; e.) hypercalciuria, leading to nephrocalcinosis and nephrolithiasis as a result of the Fanconi syndrome and vitamin D therapy; f.) aminoaciduria, glycosuria; and g.) hypokalemia.
Clinical diagnosis of Lowe syndrome should be confirmed by molecular studies of the OCRL1 gene, which unfortunately, we were unable to do due to financial constraints. Lowe syndrome is an X-linked disorder that results from loss of function of the OCRL1 protein (mutations in the gene).\textsuperscript{6,14,15} The Lowe syndrome gene was linked to markers in the Xq24-q26 region, and the locus DXS42 was the most closely linked marker.\textsuperscript{6} The OCRL1 is a lipid phosphatase that converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 4-phosphate. Mutations (deletions, frameshifts, and stop mutations, with a smaller fraction occurring as splicing and missense mutations) that cause Lowe syndrome result in the complete loss of OCRL1 catalytic activity. The OCRL1 appears to be the major PIP2-hydrolyzing enzyme in the human renal proximal tubule cells and cells lacking OCRL1 have slightly elevated levels of PIP2.\textsuperscript{15,18} This suggests that Lowe syndrome may represent an inborn error of inositol phosphate metabolism.\textsuperscript{10} Phosphatidylinositol 4,5-bisphosphate is present in cultured skin fibroblasts, but not in peripheral blood cells. Phosphatidylinositol 4,5-bisphosphate activity is markedly reduced in fibroblasts from patients with Lowe syndrome.\textsuperscript{12} Concentrations of the muscle enzymes creatine kinase, aspartate aminotransferase and lactate dehydrogenase, as well as of total serum protein, serum α2-globulin and high density lipoprotein cholesterol are elevated. Serum enzyme elevations suggest muscle involvement in the Lowe syndrome.\textsuperscript{13} Phosphoinositides (PIs) are essential phospholipids that regulate a number of processes including intracellular signaling, transport of ions and metabolites across membranes, exo- and endocytosis, regulation of the actin cytoskeleton (cytoskeletal dynamics), transcriptional regulation and membrane traffic.\textsuperscript{14}

At birth, ocular involvement with bilateral cataracts and hypotonia may be found in congenital infection (rubella), peroxisomal disorders, mitochondrialopathies, myotonic dystrophies or congenital myopathies (muscle eye brain disease). The appearance of renal involvement excludes these alternative diagnoses within the first months of life.\textsuperscript{10} Another possible diagnosis could be Dent’s disease, a rare, X-linked, renal proximal tubulopathy, but without metabolic acidosis and ocular or brain involvement.\textsuperscript{2,15,18}

The management of our patient should include ophthalmic surgery for PCO, physical rehabilitation and supplements of bicarbonate, salt (potassium) and vitamin D. Unfortunately, we were unable to give vitamin D supplementation due to financial constraints. In addition, the surgery was cancelled due to the unstable serum electrolyte levels. Treatment of Lowe syndrome includes eye, nervous system and kidney management. Cataracts should be removed early in order to avoid amblyopia. The early use of eyeglasses or contact lenses improves visual function and, consequently, psychosocial skills. The ocular tone should be tested frequently in order to diagnose glaucoma early and to treat it either with anti-glaucoma medication, or gonial or trabeculotomy surgery. Conjunctival or corneal cheloids are difficult to treat. Surgical lens implantation is not recommended, and spectacles are preferable to contact lenses.\textsuperscript{2,13} Early targeted rehabilitation therapy is necessary to treat hypotonia.\textsuperscript{13} An adequate psychological, pedagogical and occupational program may increase learning capacity and prevent frequent and serious behavioral crises during adolescence. Areflexia is a peculiar state, which does not require treatment. Seizures require treatment with drugs specific for the symptoms. The behavioral problems occurring during adolescence and the obsessive-compulsive disorder require specific competence on the part of the health staff.\textsuperscript{2} Renal tubular acidosis must be recognized and treated promptly with alkali supplements. These include citrates (sodium and/or potassium citrate) and sodium bicarbonate in various doses and combinations, to maintain serum bicarbonate levels at around 20 mEq/L. Doses may vary between 1–8 mEq/kg/day, which should be divided into at least three separate doses.\textsuperscript{12,13} Potassium citrate is particularly useful as it also helps to prevent nephrocalcinosis and tends to reduce renal calcium excretion. If polyuria is present, patients should receive supplementary fluid. Sodium intake should be adjusted according to the extent of renal salt loss. In infants and very young children, oral supplements should be promptly adjusted in case of diarrhea. Intravenous infusions may be needed. Rickets should be treated with oral phosphate supplements and vitamin D. Excessive amounts of vitamin D should be avoided as they may increase renal calcium excretion. Treatment should be targeted towards maintaining serum calcium and
parathormone (PTH) levels within normal range and serum phosphate levels above 2–2.5 mg/dL. Genetic counseling should be done for carrier detection and prenatal testing, as the mother has a 25% possibility of having an affected son and a 25% possibility of having a carrier daughter. Molecular analysis of the OCRL1 gene is a more specific way to diagnose female carriers if the mutation in the proband is known. Genetic mutations should be documented first in the proband. As many as 94% of female carriers may be detected during ophthalmologic examination by slit-lamp biomicroscopy. The typical findings are multiple punctuate lenticular opacities or a single, dense posterior cataract. However, even if the mother has normal ocular findings, mutation analysis should still be done because some women are non-penetrant carriers and do not have the characteristic eye manifestations, albeit rarely. The longest reported survival was that of a 54-year-old patient. Death usually occurs between the end of the second decade and the beginning of the fourth decade of life. The most common cause of death is renal tubulopathy, progressively evolving into renal insufficiency. Patients’ quality of life depends on the extent of their mental and renal manifestations. Some patients may enjoy a discrete social life and assisted working activity. Early diagnosis and treatment of metabolic disturbances may delay the morbidity and mortality in this syndrome.4,11,12

Conflict of interest

None declared.

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