Lowe syndrome: case report

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Abstract

Lowe syndrome is a rare X-linked multisystemic disorder, caused by mutation of the *OCRL* gene which encodes OCRL-1 protein. The disease is characterized by the triad of congenital cataracts, intellectual disability, and Fanconi-like proximal renal tubular dysfunction. Lifespan is short due to end-stage renal disease and other earlier complications and it rarely exceeds 40 years. The treatment is symptomatic, aimed at improving the clinical evolution of the patients and postpone the onset of terminal renal disease. The paper describes a case of a boy with Lowe syndrome with a novel genetic mutation.

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1. Introduction

Lowe syndrome, also known as oculocerebrorenal syndrome is a rare X-linked recessive multi-systemic disorder. Lowe syndrome is characterized by congenital cataracts, involvement of the central nervous system with neonatal and infantile hypotonia with subsequent mental impairment, and proximal renal tubular dysfunction of the Fanconi type which usually develops within first few months of life. The life span of affected individuals is importantly shortened and rarely exceeds 40 years, mostly because of progressive electrolyte and bicarbonate wasting through kidneys and chronic kidney disease with complications. The leading cause of death in childhood is pneumonia due to hypotonia and poor cough reflex and gastrointestinal infections. Other causes of death include status epilepticus, sudden unexplained death in sleep and severe dehydration due to Fanconi syndrome and kidney failure. The prevalence of Lowe syndrome has been estimated to be 1 in 500,000 in the general population, based on the observations of the American Lowe Syndrome Association and the Italian Lowe Syndrome Association (1). The estimated prevalence of the syndrome is much lower in other countries, probably due to the poor recognition of the disease and subsequent underdiagnosis (1,2).

Specific clinical signs of the syndrome were first reported in 1952. Later the disease was proved to be caused by mutations in the *OCRL* gene on chromosome Xq 26.1, which encodes the enzyme phosphatidylinositol (4,5)-biphosphate (OCRL-1) located in the trans-Golgi network. OCRL-1 is expressed in all human cells except in the cells of hema-

topoietic origin, and contains 24 exons, exon 1 being a non-coding exon. Defects of OCRL-1 lead to increased intracellular levels of phospholipid phosphatidylinositol biphosphate, which plays an important role in cell signalling, protein trafficking and actin polymerisation. Gene mutations are detected in 95 % of patients with Lowe syndrome. De novo mutations are present in approximately 32 % of males with Lowe syndrome. Other cases are transmitted from maternal carriers, who, except for punctate lens opacities in adulthood, usually do not develop other clinical signs of the disease (1,3).

So far, more than 200 different gene mutations with heterogeneous phenotypic manifestations have been described. This may be the reason for the difficulty in diagnosis and subsequent treatment delay, which is, despite being symptomatic, important for the prevention or at least postponement of late complications, especially end-stage renal disease (1).

The diagnosis is established using molecular genetic testing – DNA analysis of the isolated patient's peripheral blood sample or by demonstrating reduced (< 10 % of normal) OCRL-1 activity in cultured skin fibroblasts (4).

This paper describes a case of a boy with Lowe syndrome with a novel genetic mutation in the *OCRL* gene.

2. Case presentation

A newborn boy at the age of 11 hours was transferred from the Maternity Hospital Postojna to the Department of Neonatology at the Children's Hospital in Ljubljana due to hypotonia and dysplastic features. The baby was born at completed 38 weeks of gestation following the fourth uneventful pregnancy which was monitored in Kosovo.

Family history revealed data about early death of a few male family members who had abnormal neurological signs. The boy's mother had three older brothers who died in early childhood and were all hypotonic and blind. The first born of the boy's parents had the same clinical features and died at the age of six. The boy has two older brothers, one had epilepsy in early childhood, the other is completely healthy. There was no reported consanguinity in the family.

The boy was treated with oxygen supplement for a few days after birth due to respiratory distress which was considered to be due to decreased muscle tone after all other possible causes had been excluded. At that time he also received transient oral therapy with theophylline. The first basic laboratory blood analysis was normal.

Due to abnormal neurologic signs, ultrasound (US) and magnetic resonance imaging (MRI) of the head were performed during hospitalisation at the Department of Neonatology. MRI revealed a central nervous system developmental anomaly with myelination disorder, hypoplastic cerebellum, dilatation of the lateral ventricles, fourth ventricle and cisterna magna, and slightly hypoplastic pons. Due to pathological electroencephalography findings and seizures, phenytoin therapy was started. Electromyographic findings were borderline pathological due to decreased speed of motor conduction and reduced motor units' amplitude potentials. Auditory brain stem response (ABR) with audiometry revealed moderate bilateral sensorineural hearing loss. Ophthalmologist confirmed the presence of bilateral congenital cataract. Ultrasonography of the hips was normal despite severe hypotonia. Heart and abdominal ultrasound did not reveal any pathology. Laboratory blood tests were normal, including nor-

mal kidney function, only creatinine kinase levels were slightly elevated (7.87 µkat/L, normal: 0.68–5.5 µkat/L for babies up to 6 months). According to all clinical signs and findings, Muscle-eye-brain disease was suspected. Numerous molecular genetic tests were done, e.g. karyotyping, analysis of subtelomeric chromosome regions and fluorescence in situ hybridisation analysis of the q11.1–13 chromosome region for Prader-Willi syndrome detection. The tests revealed normal male karyotype and no other specific changes detectable by these tests. Newborn screening for possible metabolic disorders using tandem mass spectrometry, performed in a German laboratory was normal.

The boy underwent surgery of cataracts removal at the age of two months; artificial lenses were not implanted. Because of glaucoma two-drug topical treatment and oral treatment with acetazolamide was started for reducing intraocular pressure. At the same age, he was admitted to the Department of Nephrology of the Children's Hospital in Ljubljana for the first time for inappetence and possible urinary tract infection. He was afebrile on admission, with signs of upper respiratory tract infection. Native urine sample analysis revealed proteinuria (2–3+) and microscopic haematuria (6–20 erythrocytes in sediment), while serum albumin levels (47 g/L; normal: 35–45 g/L) and protein levels in serum (73 g/L; normal: 57–80 g/L) were normal. Abdomen and urinary tract ultrasound scan was again perfectly normal. Three different types of bacteria were isolated from the urine culture (*S. aureus* with 10^5 colony-forming units (CFU)/ml, *E. coli* and *K. oxytoca* with 10^4 CFU/ml). Because of suspected urinary tract infection, the boy received oral antibiotic therapy. At the age of three months, urine analysis again revealed proteinuria and microscopic haematuria, suspected to be caused by high urinary excretion of calcium; calcium/creatinine ratio being 3.25 (95th percentile for infants up to 7 months is 2.42). High urinary excretion of calcium was thought to be caused by boy's poor hydration and borderline elevated serum calcium levels, which were 2.67 mmol/L (normal: 2.1–2.6 mmol/L). At the next check-up only mild microscopic haematuria without proteinuria persisted.

At the age of four and a half months the boy was again admitted to the Children's Hospital in Ljubljana for dehydration while recovering from type A influenza virus infection. On admission, elevated serum levels of urea (12.4 mmol/L; normal: 2.8–6.7 mmol/L) and creatinine (94 mmol/L; normal: 22–88.4 mmol/L) were recorded. We noted normalisation of these levels after appropriate rehydration (urea: 2.8–4.3 mmol/L and creatinine: 19–40 mmol/L); serum protein levels (68 g/L) and albumin levels (39 g/L) were also in the normal range. On the contrary, hypokalaemia (2.4–3.8 mmol/L; normal: 3.8–5.5 mmol/L) and metabolic acidosis (pH 7.28, HCO_3^- 14.8 mmol/L and BE -11 mmol/L) persisted, with urine pH persistently above 5.5 and positive urine anion gap (16 mmol/L). Symptomatic treatment of hypokalaemia and metabolic acidosis was introduced. At that time, we recorded severe hypophosphatemia for the first time (0.53–0.65 mmol/L; normal: 0.8–2.1 mmol/L), therefore the therapy with oral phosphate powder supplements was started. Low serum magnesium levels were also present (0.46 mmol/l; normal: 0.6–1.10). Later we recorded episodic glucosuria, and another episode of proteinuria and microscopic haematuria. Urine protein/creatinine ratio (U-P/C) was 1695 mg/mmol of creatinine (normal levels for infants 6–24 months are up to 50 mg/

mmol). The proteinuria was classified as selective glomerular with tubular proteinuria (U-P/C = 1765 g/mol, U-alpha-1-microgl./C = 1013.33 g/mol (normal up to 1.58 g/mol), U-IgG/Creatinine = 184.33 g/mol (normal up to 1.13 g/mol), U-Albumin/Creatinine = 846.67 g/mol (normal up to 2.26 g/mol), Q U-IgG/U-Alb = 0.22). These results indicated a renal tubular disorder with the associated glomerular disease, which was at first thought to be a transient condition following the acute renal failure due to dehydration while recovering from the influenza virus. According to the laboratory results (hypophosphataemia, glucosuria, pronounced tubular proteinuria) proximal tubular disorder was suspected. The repeated urinary tract ultrasound scan was normal, with no signs of nephrocalcinosis or renal calculi. Because of feeding difficulties and poor weight gain nasogastric tube was inserted and hypercaloric intake was started. His weight gain improved.

Despite acetazolamide and phenytoin discontinuation and bicarbonate supplements, metabolic acidosis persisted. Therefore, at the age of six months the boy was admitted again to the Department of Nephrology of the Children's Hospital in Ljubljana for further diagnostic procedures of renal tubular acidosis, proteinuria (0.62 g in 24-hour urine sample = 120 mg/m^2/h), hypokalaemia, hypophosphataemia and occasional hypomagnesaemia. Calcium urine excretion (3.2 mg/kg/day; normal: up to 4 mg/kg/day) and calcium serum levels were normal. According to the laboratory findings and clinical signs Lowe syndrome was suspected. We performed molecular genetic testing in the Genetic Diagnostic Laboratory, Vrazov trg, Ljubljana, where a mutation on the *OCRL* gene was found – c.812T > A hemizygous nucleotide change in exon 9, which transforms amino acid isoleucine into asparagine at position 271. Until then, this mutation was not described in the HGMD base (Human Gene Mutation Database) or the SNP base (single nucleotide polymorphisms) of OCRL gene polymorphisms yet, but according to *in silico* methods the mutation was predicted to be pathological. Determination of the mutation segregation revealed that the boy's mother was the mutation carrier, but it was not found in the boy's father.

Severe global developmental delay and hypotonia have always been noticed in neurological examinations. The boy has regular appointments with ophthalmologist for regular following after congenital cataracts operation and glaucoma, with neurologist because of developmental delay, with gastroenterologist because of feeding difficulties and poor weight gain (recently percutaneous endoscopic gastrostomy tube was inserted), with endocrinologist because of osteoporosis and short stature, and with nephrologist because of proximal tubular disease with subsequent severe metabolic acidosis, hypokalaemia and hypophosphataemia. Raised levels of lactate dehydrogenase have also been recorded at all times (between 7.04 and 8.18 μkat/l, normal: 2.59–5.76 μkat/l for boys 1–3 years of age).

Figure 1 shows the boy's growth and weight gain. The percentiles of both measurements were within the average range according to the general population at the boy's birth, growth delay and poor weight gain became apparent only later.

The boy regularly receives electrolyte supplements (phosphate powder and potassium chloride), therapy for metabolic acidosis correction (sodium bicarbonate and Uralyt – Na and K citrate), combination of potassium-sparing diuretic amiloride and diuretic thiazide,

which lowers calcium urinary excretion and prevents renal calculi formation. He also receives topical therapy for glaucoma, proton pump inhibitor pantoprazole, osteoporosis treatment (vitamin D and calcium citrate) and supplements for nervous system protection (vitamin B complex, L-carnitine, coenzyme Q).

3. Discussion

Clinical manifestation of Lowe syndrome depends, besides a specific mutation in the *OCRL* gene on the Xq 26.1 chromosome, on the patient's age. At birth and during the neonatal period patients present with severe muscle hypotonia with hyporeflexia, dense bilateral cataracts and eventual high levels of creatinine kinase or lactate dehydrogenase. At this age, renal dysfunction is not yet apparent, therefore generalized congenital infections (e.g. rubella), mitochondrial disorders, peroxisomal biogenesis disorders or congenital muscle dystrophies with muscle, eyes and nervous system involvement (e.g. Muscle-eye-brain disease, suspected also in our patient) should be considered in the differential diagnosis (4).

Incomplete Fanconi syndrome manifestations (bicarbonaturia with acidosis, aminoaciduria and phosphaturia) are usually not recognised or appear only later in life, usually between the ages of 3 and 12 months; they progress gradually and may lead to end-stage renal disease between the second and third decade of life through progressive glomerulosclerosis (1,4). Lowe syndrome is a multisystem disorder which involves:

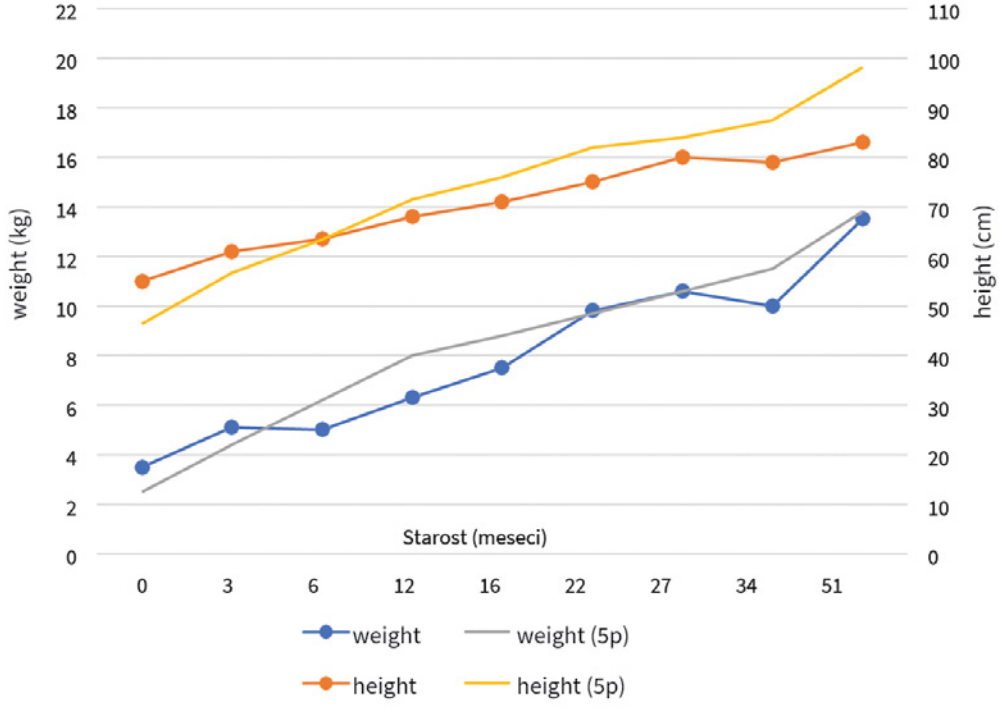

Figure 1: Patient's body mass and height at different ages according to the 5th percentile in the general population.

3.1. Central nervous system

Neurological signs manifest and worsen with age with severe developmental delay (average IQ 40–45) (1), behavioural abnormalities and seizures in 50 % of patients (4). MRI changes are non-specific and may include ventriculomegaly (as in the described case) and hyperintense periventricular lesions (1,5).

3.2. Eyes

Eye involvement is a hallmark of Lowe syndrome and begins early in the embryogenesis with defective formation and subsequent degeneration of posterior lens fibres and cataracts development. These require early operation and prescription of eyeglasses (artificial lens implants are contraindicated), although visual acuity remains poor (rarely more than 20/100) due to retinal dysfunction. Secondary glaucoma, corneal scarring and keloid formation may develop which require regular check-ups with ophthalmologist (1,4).

3.3. Kidneys

Renal dysfunction is one of the most threatening conditions of this syndrome. It manifests as proximal tubulopathy with low molecular-weight proteinuria which is observed in all patients with Lowe syndrome. Retinol-binding protein, *N*-acetyl-ß-D-glucosaminidase, α_1-microglobulin and β_2-microglobulin are highly sensitive markers of this renal tubular dysfunction. The reason for this type of proteinuria is defective endocytosis via the megalin and cubilin receptors in the renal proximal tubule due to actin accumulation on endosomal membrane. Defective reabsorption via the megalin receptor pathway also causes albuminuria with normal serum albumin concentrations. Total proteinuria is in the nephrotic range (> 1 g/m^2/day) in more than one half of the patients (1).

Generalized aminoaciduria is observed in around 80 % of patients with Lowe syndrome (1).

Hypercalciuria is also a common feature, although its pathophysiology has not yet been fully elucidated. Nephrocalcinosis or nephrolithiasis is present in one half of the patients, unrelated to calciuria. Stones are composed of calcium oxalate and calcium phosphate. Some studies report successful use of thiazide diuretics for treatment or prevention of renal stone formation, with strict monitoring of hypokalaemia, hyponatraemia and hypovolaemia as possible drug's side effects (1,6).

Hyperchloremic metabolic acidosis is a common finding, yet plasma carbon dioxide concentration is at the lower end of the normal in almost all patients (7).

Data on the prevalence of phosphaturia varies in the literature. Patients with phosphaturia need phosphate supplements, or hypophosphatemic rickets will develop in 50 % of patients by the age of 1 year (1,7).

The described electrolyte disturbances and metabolic acidosis could also be the adverse effect of certain medications, e.g. acetazolamide and phenytoin, which our patient also received. Laboratory findings could therefore be falsely attributed to side effects of medications, which might delay the diagnosis of renal dysfunction. But specific laboratory results persisted despite medications discontinuation, and so did proteinuria and glucosuria, indicating a proximal renal tubular dysfunction. That is why we continuously monitored the patient's condition and the correct diagnosis was quickly set.

Pathogenesis of progressive renal failure is not yet entirely clear, but glome-

rulosclerosis and tubulointerstitial fibrosis probably result from a chronic renal tubular injury, which leads to end-stage renal disease in the second to fourth decade of life (1,4). Renal function starts to decrease at around ten years of age (8), and glomerular filtration rate values are used for following its progression. The glomerular filtration rate is calculated with adjusted formula due to lower muscle mass of patients with Lowe syndrome. Progression of the real disease is also clearly seen on renal biopsy, which is normal until the age of two, later followed by tubular dilatation with proteinaceous casts, focal glomerular sclerosis and diffuse tubulointerstitial fibrosis (1).

The decision to initiate dialysis is medically and ethically complex and depends on the degree of developmental delay, general medical condition, family support and social status. A small number of selected individuals have been treated successfully with haemodialysis, peritoneal dialysis, and renal transplants over a few years according to their doctors' personal observations. However, no data about long-term outcomes is available (4,5).

3.4. Do patients with Lowe syndrome have Fanconi syndrome?

Fanconi syndrome is the main reason for proximal renal tubular acidosis in children, caused by inherited (most often cystinosis) or acquired disorders (drugs and heavy metals toxicity). Generalised proximal tubular dysfunction leads to phosphaturia, glucosuria, aminoaciduria, low molecular-weight proteinuria, and proximal tubular acidosis. Lowe syndrome is a genetic disorder which also has characteristic features, connected to Fanconi syndrome (9). The difference between patients with Lowe syndrome and patients with other forms or causes of Fanconi syndrome is decreased production of ammonia and extremely rare incidence of glucosuria. These are the reasons that some authors think that Lowe syndrome should rather be classified as selective proximal tubulopathy or "incomplete Fanconi syndrome" (7,10).

3.5. Other manifestations

Osteopenia is almost universally present in patients with Lowe syndrome and may lead to repeated pathologic bone fractures, especially along with untreated metabolic acidosis and renal phosphate wasting. Treatment with vitamin D is often required to normalize increased parathyroid hormone levels. Intravenous pamidronic acid treatment may help to normalise decreased bone density. Arthritis, arthropathy and tenosynovitis have been reported in one--half of the patients over 20 years of age (1,4).

Unrelated with bone disease or renal disease stage, severe growth delay and poor weight gain are present, the features also found in our patient (5). In the study, in which the described patient was also included (8), the correlation between acidosis and growth delay was reported - patients with uncorrected or poorly corrected acidosis were significantly shorter than their peers without acidosis.

After recognition of bleeding disorders in patients with Lowe syndrome, specific blood analyses revealed early platelet activation disorders (adhesion) with normal values of other platelet aggregation tests. In addition, mild thrombocytopenia has been noted in around 20 % of patients (1,4,5), which we have not found in our patient by now.

In the literature as well in our patient certain occasional abnormalities of laboratory findings have been reported – elevated serum concentration of high--density cholesterol, creatinine kinase, liver enzymes and lactate dehydrogenase , but they are still of uncertain significance (4,5).

Cryptorchidism, which occasionally requires surgical intervention, has been reported in about one third of patients (1,4).

Benign cystic lesions of the skin have also been reported, probably due to increased extracellular concentrations of lysosomal enzymes (1). We have not seen them in the presented case by now.

4. Conclusions

Lowe syndrome is difficult to diagnose, the diagnosis being usually is delayed due to its rare incidence and incomplete clinical manifestation in early life. Patients with Lowe syndrome require multidisciplinary treatment due to varying clinical problems. Treatment is mostly symptomatic and has to be carefully planned due to continuous renal losses, and at the same time ethically rational and minimally burdensome for patients and their parents. Early diagnosis is important for early treatment initiation, and also for the early possibility of genetic counselling and further family planning for the patient's family members.

The boy's parents approved the publication of the present article.

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