Pediatr Pol 2024; 99 (1): 89-93
DOI: https://doi.org/10.5114/polp.2024.135847
Submitted: 09.05.2023, Accepted: 14.07.2023, Published: 05.03.2024

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

CASE REPORT

Clinical overlap and diagnostic difficulties in a patient with Lowe syndrome

Adam Jan Strzoda[1], Aleksandra Sobieszczańska-Droździel[2], Magdalena Kamińska[1]

[1]Student's Scientific Group at the Department of Paediatric Nephrology, Medical University, Lublin, Poland
[2]Department of Paediatric Nephrology, Medical University, Lublin, Poland

ABSTRACT

Lowe syndrome (oculocerebrorenal syndrome of Lowe – LS) is an ultra-rare, recessive X-linked, multisystem disorder that primarily occurs in males and affects the eyes, nervous system, and kidneys. It is a consequence of mutation of the *OCRL* gene on chromosome Xq25-26, which encodes phosphatidylinositol 4,5-bisphosphate 5 phosphatase, a protein present in the Golgi complex, lysosomes, and endosomes. The most common symptoms of LS involve congenital cataracts, neurological retardation, and incomplete Fanconi syndrome, ultimately leading to end-stage renal disease between the second and fourth decade of life. The authors present a boy with the intoxication of vitamin D_3 and suspicion of congenital cytomegaly eventually diagnosed with LS at the age of 16 months.

KEY WORDS:

renal proximal tubulopathy, vitamin D_3 hypervitaminosis, Lowe syndrome.

INTRODUCTION

The identification of patients with an ultra-rare disease is a diagnostic challenge, particularly when other disorders with symptoms overlapping its phenotype coexist. Sometimes only intuitive hunches, followed by analytical reasoning, make an accurate diagnosis possible. In contrast to routine practice, the art of differential diagnosis is to recognise crucial patterns of symptoms, manipulate the probabilities, and select the most accurate cause of the patient's condition. The authors present a 2.5-year-old boy with Lowe syndrome (LS) caused by a pathogenic variant in the *OCRL1* gene diagnosed at the age of 16 months. Vitamin D_3 overdosing and suspicion of congenital human cytomegalovirus (CMV) mimicked symptoms of LS delayed an accurate diagnosis.

STATEMENT OF ETHICS

Written informed consent to publish the case with accompanying images was obtained from the parents of the affected patient.

CASE REPORT

We report on a 2.5-year-old boy of Polish descent referred to the Department of Paediatric Nephrology at the age of 8 months due to nephrocalcinosis, considered a consequence of vitamin D_3 toxicity. The patient is the first child of non-consanguineous healthy parents born in the 37th week of pregnancy by caesarean section due to foetal arrhythmia. The pregnancy was complicated by the mother's flu-like infection in the first trimester, while the family history was uneventful. Apgar score was 10, body weight and length, and head circumference were 3300 g (25%), 55 cm (90%), and 32 cm (2%), respectively. At the age of 3 months, the parents observed nystagmus and a lack of fixation. A binocular cataract was then diagnosed and operated on soon after. Global hypotonia, psychomotor retardation, and poor weight gain prompted the mother to increase his vitamin D_3 daily dose to 2000 IU at the age of 5 months. Due to clinical deterioration, diagnostics were carried out in local hospitals. Congenital CMV, anaemia, hypercalcaemia (max 3.55 mmol/dl), 25-hydroxy-cholecalciferol (25-OHD_3) increased > 100 ng/ml, parathormone decreased

ADDRESS FOR CORRESPONDENCE:

Adam Jan Strzoda, Student's Scientific Group at the Department of Paediatric Nephrology, Medical University, Lublin, Poland, e-mail: adamjanstrzoda@gmail.com

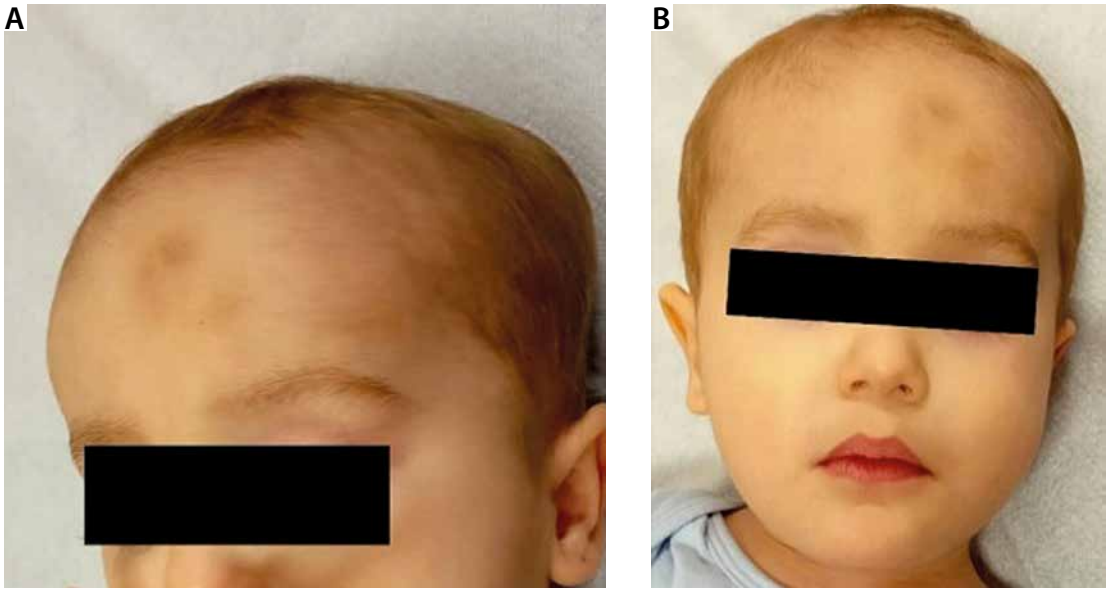

FIGURE 1. The face of the presented patient. Note the dysmorphic features – wide forehead and prominent frontal eminences – and bruises on the forehead

to 4 pg/ml, leukocyturia (20–30 WBC/HPF), and proteinuria (150 mg/dl) considered as urinary tract infection were found. The ultrasound revealed nephrocalcinosis, and consequently the patient was referred to the Department of Paediatric Nephrology. On admission, his length, weight, and head circumference were < 3% (76 cm, 6.3 kg, and 42.4 cm, respectively). The physical examination revealed global hypotonia, umbilical hernia, pectus excavatum, and facial dysmorphia with a wide forehead, prominent frontal eminences, deeply set eyeballs, and eyes slanted upwards (Figure 1).

Intoxication with vitamin D_3 was confirmed and successfully treated (normalisation of calcaemia and cholecalciferol metabolites). Microcytic anaemia with low iron level and transferrin saturation index but normal ferritin required supplementation of haematopoietic drug: iron and B vitamins. On the follow-up, sterile leukocyturia occurred periodically (Table 1).

Red blood cells, mean corpuscular volume, were 1,25-OHD_3: 1,25-dihydroxyvitamin D_3, 25-OHD_3: 25-hydroxyvitamin D_3, lactate dehydrogenase, aspartate aminotransferase, creatine kinase.

Increasing serum CMV IgG (50.9–78.9 U/ml) and the presence of CMV DNA in urine (5.6 ´ 105 IU/ml) and blood (7.8 ´ 102 IU/ml) were found. Conversely, CMV DNA was absent in the cerebrospinal fluid (CSF), and magnetic resonance (MRI) of the head and orbital cavities showed no significant abnormalities, which ruled out the previously suspected congenital cytomegaly. Amino acids and lactates in both serum and CSF were normal as well as GC-MS-based urinary organic acid profiling. Spinal muscular atrophy (SMA) and celiac disease were excluded. The result of microarray-based comparative genomic hybridisation was irrelevant. The features of incomplete Fanconi syndrome, such as persistent proteinuria of, hypercalciuria, aminoaciduria, and finally at the age of 2 metabolic acidosis (HCO_3 – 20.7 mmol/l, BE – 4.1 mmol/l) were treated symptomatically with hydrochlorothiazide (0.4 mg/kg/day) and bicarbonates (80 mg/kg/day). Simultaneously an energy-rich diet was introduced. Suspected at the time, LS was not primarily confirmed by analysis of exon 15 in the *OCRL1* gene at the age of one year. However, 4 months later the whole-exome sequencing revealed a hemizygous novel pathogenic variant c.832C > G in the *OCRL1* gene and confirmed the initial diagnosis. The same heterozygous mutation was found in the proband's mother.

Currently, at 2.5 years old, ultrasonographic features of bilateral nephrocalcinosis remain stable in the second stage according to Hoyer's ultrasound staging. Additionally, a 5 mm long stone was found in the middle calyx of the right kidney (Figure 2). The boy's weight, height, and head circumference are < 3% (80 cm, 9.1 kg, and 44 cm, respectively). The patient presented global hypotonia and psychomotor retardation as he began to sit down, stand up, and walk (with assistance) at the age of 18 months, 20 months, and 22 months, respectively. Mental and speech development remains moderately impaired. He does not report physiological needs, uses single words, and presents auto-aggressive behaviour – impulsive head-hitting (Figure 1). Multi-specialty care, personalised, intensive rehabilitation, and eyepiece correction are necessary. The patient is treated symptomatically with hydrochlorothiazide, sodium bicarbonate, and potassium chloride.

DISCUSSION

Lowe syndrome (oculocerebrorenal syndrome of Lowe – *OCRL*, OMIM #309000) is an ultra-rare X-linked recessive multisystem disorder with a prevalence of 1 : 500,000 in the general population. It primarily occurs in males and is caused by mutations in the *OCRL1* gene on

TABLE 1. Follow-up of selected laboratory results in the presented patient

Labaratory parameters	Admission	3-months follow-up	9-months follow-up	18-months follow-up	23-months follow-up	Reference range
Blood						
RBC [x106/ul]	4.3	5.02	5.42	5.61	5.38	4.2–5.1
Haemoglobin [g/dl]	8.6	9.9	11.6	13.1	13.1	10.1–12.7
MCV [fl]	65.1	62.4	67.2	70.8	76.2	76.5–90.6
Haematocrit (%)	28	31.3	36.4	39.7	41	33–40
Parathormone [pg/ml]	4.73	5.36	16.51	32.64	37.74	10–65
Serum						
1,25-OHD3 [pg/ml]	103	55.4	–	–	–	25–86.5
25-OHD3 [ng/ml]	93.6	49.3	38.1	29.7	27.6	20–60
Iron [ug/dl]	53	52	82	56	–	27–109
Transferrin saturationindex (%)	10	–	21	–	–	20–50
Ferritin [ng/ml]	299	51.2	47.7	96.9	–	14–124
Calcium [mmol/l]	2.79	2.73	2.58	2.63	2.45	2.25–2.75
Phosphates [mmol/l]	1.2	1.38	1.46	1.46	1.29	1.15–2.15
Kalium [mmol/l]	4.3	4.06	4.29	4.28	4.69	3.5–5.1
Creatinine [mg/dl]	0.25	0.27	0.29	0.3	0.26	0.17–0.42
LDH [U/l]	737	–	–	–	–	279–339
AST [U/l]	105	86	105	103	99	0–39
CK [U/l]	100	–	–	–	9	0–203
Blood gases						
pH	7.4	7.43	7.37	7.35	7.34	7.35–7.45
HCO_3 [mmol/l]	21.9	21.7	21.5	20.7	18.4	22.5–30
Urine						
Specific gravity [g/ml]	1.005	1.005	1.005	1.005	1.000	1.015–1.030
Glucose [mg/dl]	0	0	0	0	0	0
Protein (mg/dl)	78.5	28.7	36.9	139.8	97.4	0–15
pH	8	7	8	8	8.0	5–7
Erythrocytes (*n per* high power field)	1–3	0	0	0	30–50	0–5
Leukocytes (*n per* high power field)	50–70	5–10	20–30	1–3	1–3	0–5
Calcium to creatinine ratio [mmol/mmol]	2.5 (normal range: 0.09–2.2)	5.36(normal range: 0.07–1.5)	5.25 (normal range: 0.07–1.5)	1.6 (normal range: 0.06–1.4)	–	Age-dependent

1,25-OHD3 – 1,25-dihydroxyvitan D3, 25-OHD3 – 25-hydroxyvitamin D3, AST – aspartate aminotransferase, CK – creatine kinase, LDH – lactate dehydrogenase, MCV – mean corpuscular volume, RBC – red blood cells

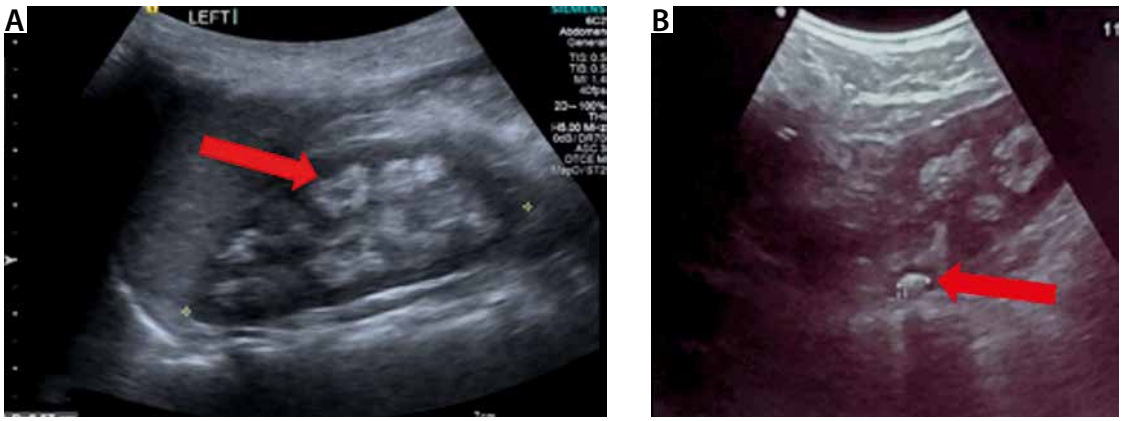

FIGURE 2. Renal ultrasounds of the presented patient at the age of 2.5 years (**A** – left, **B** – right). Arrows indicate nephrocalcinosis (**A**) and kidney stone (**B**)

chromosome Xq26-25, which encodes phosphatidylinositol 4,5-bisphosphate 5 phosphatase, the protein primarily present in the Golgi complex, lysosomes, and endosomes [1–4]. The *OCRL1* gene is believed to be responsible for various cellular processes; however, membrane trafficking and actin cytoskeleton remodeling seem to be the most important. Proximal tubular cells, neurons, and lens epithelial cells have above-average rates of endocytosis and are therefore prone to loss of *OCRL1* gene function [3, 4]. Consequently, in patients with LS, the eyes, nervous system, and kidneys are mainly affected [1–3]. Typical clinical manifestations include infantile glaucoma, congenital cataracts, areflexia, muscular hypotonia, intellectual disability, and renal proximal tubulopathy, ultimately leading to end-stage renal disease (ESRD) between the second and fourth decades of life [1]. Mathematic and animal models suggest that the pathogenic variants in the *OCRL1* gene impair the regeneration of proximal tubules, which leads to their shortening and could explain renal symptoms such as low-molecular-weight proteinuria, aminoaciduria, hypercalciuria, and renal tubular acidosis [4]. Thus, persistent proteinuria and hypercalciuria, observed in the presented patient from the first admission to our department, are typical renal manifestations of LS. Due to the abnormal muscle metabolism of our patient, elevated lactate dehydrogenase, serum creatinine kinase, and aspartate transaminase were partially observed, which are typical for LS (Table 1). Later, at the age of 2 years, metabolic acidosis completed the clinical picture. The correct diagnosis was initially blurred by overlapping symptoms caused by a vitamin D_3 overdose. Hypercalciuria in the presented patient could be associated with vitamin D_3 intoxication as well as nephrocalcinosis, although the latter is rarely observed (about 10% of cases) [5]. The latest Polish recommendations on daily intake of cholecalciferol for children 0–5 months old are 400 IU/day and for 6–12 months 400–600 IU/day [6]. The dose taken by the presented patient was 5 times higher, and similar cases described in the literature resulted in hypercalcaemia and hypercalciuria [7]. The overdosing was confirmed by the toxic level of 25-OHD_3 and decreased parathyroid hormone level.

Hypercalcaemia and low parathormone are not observed in LS, while urolithiasis and nephrocalcinosis are found in about 22% and 52% of patients, respectively [8]; both may lead to sterile leukocyturia observed periodically in the presented patient [9].

Interestingly, the congenital cataract observed in our patient together with the high titre of serum anti-CMV IgG (50.09 U/ml) and the presence of CMV DNA in urine and blood suggested perinatal CMV infection, which is an obvious cause of a cataract [10, 11]. Moreover, 1 in 3 cases of congenital cataracts is not a consequence of the systemic disorder, so the binocular cataract in our patient was initially linked to cytomegaly [12]. Further research revealed the absence of CMV DNA in the CSF and the lack of characteristic abnormalities in the brain MRI, which indicated postnatally acquired cytomegalovirus infection. Other symptoms present in our patient and common in infants with congenital CMV infection include anaemia, mental retardation, and microcephaly [11]. Our patient's mother had a high titre of anti-CMV IgG (414 U/ml) and negative anti-CMV IgM (0.14 U/ml) in the first trimester. Thus, with high probability, we can rule out the mother's CMV infection during pregnancy.

The first genetic testing for LS was negative and directed the diagnostic reasoning toward another cause of symptoms observed in the presented patient, such as poor neurodevelopment, hypotonia, and low weight gain. Consequently, SMA, celiac disease, galactosemia, and other metabolic diseases were ruled out. The pathogenic variants of the *OCRL1* gene include deletion, missense, and nonsense mutations that may relate to the different parts of the gene resulting in various genotypes and phenotypes [13]. Moreover, even the affected members of the same family may present different symptoms, and the correlation between the type of mutation and the severity of the disease is not confirmed [14]. Many symptoms of LS are nonspecific and appear only in some of the affected patients.

Our patient had prominent frontal eminences and deeply set eyeballs (Figure 1) which are typical in LS; however, other characteristic symptoms such as dental anomalies, tendonitis, and cryptorchidism were not observed in the presented patient [2]. Although the prognosis in LS is uncertain, the disease inevitably leads to ESRD. The treatment is mostly symptomatic, and multidisciplinary care with extensive rehabilitation are necessary.

CONCLUSIONS

The presented case shows diagnostic difficulties in a patient with LS and overlapping comorbidities. Comprehensive analysis of clinical symptoms and detailed genetic evaluation enabled correct diagnosis and appropriate management.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Loi M. Lowe syndrome. Orphanet J Rare Dis 2006; 1: 16.
2. Bökenkamp A, Ludwig M. The oculocerebrorenal syndrome of Lowe: an update. Pediatr Nephrol 2016; 31: 2201-2212.
3. Mehta ZB, Pietka G, Lowe M. The cellular and physiological functions of the Lowe syndrome protein OCRL1. Traffic 2014; 15: 471-487.
4. Gliozzi ML, Espiritu EB, Shipman KE, et al. Effects of proximal tubule shortening on protein excretion in a Lowe syndrome model. J Am Soc Nephrol 2020; 31: 67-83.
5. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, et al. Vitamin D toxicity-a clinical perspective. Front Endocrinol (Lausanne) 2018; 9: 550.

6. Płudowski P, Kos-Kudła B, Walczak M, et al. Guidelines for preventing and treating vitamin D deficiency: a 2023 update in Poland. Nutrients 2023; 15: 695.
7. Talarico V, Barreca M, Galiano R, et al. Vitamin D and risk for vitamin A intoxication in an 18-month-old boy. Case Rep Pediatr 2016; 2016: 1395718.
8. Zaniew M, Bökenkamp A, Kolbuc M, et al. Long-term renal outcome in children with OCRL mutations: retrospective analysis of a large international cohort. Nephrol Dial Transplant 2018; 33: 85-94.
9. Szmigielska A, Krzemień G. Sterile leukocyturia – difficult diagnostic problem in children. Dev Period Med 2017; 21: 139-143.
10. Mansoor N, Mansoor T, Ahmed M. Eye pathologies in neonates. Int J Ophthalmol 2016; 9: 1832-1838.
11. Chiopris G, Veronese P, Cusenza F, et al. Congenital cytomegalovirus infection: update on diagnosis and treatment. Microorganisms 2020; 8: 1516.
12. Zetterström C, Kugelberg M. Paediatric cataract surgery. Acta Ophthalmol Scand 2007; 85: 698-710.
13. Lin T, Orrison BM, Leahey AM, et al. Spectrum of mutations in the OCRL1 gene in the Lowe oculocerebrorenal syndrome. Am J Hum Genet 1997; 60: 1384-1388.
14. Zhou FQ, Wang QW, Liu ZZ, et al. Novel mutation in OCRL leading to a severe form of Lowe syndrome. Int J Ophthalmol 2019; 12: 1057-1060.