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Lowe syndrome (Oculocerebrorenal Syndrome): A case report

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Abstract
Lowe syndrome (Oculocerebrorenal syndrome of Lowe) is a rare X-linked recessive disorder characterized by the involvement of the eyes, brain, and kidneys. The causative gene is OCRL1. Survival rarely exceeds 40 years. I am reporting on a two-month-old male infant who presented for a 2-month vaccination visit, and was found to have an eye problem (cataract), a brain problem (hypotonia with MRI finding of hypoxic ischemic encephalopathy), and renal problems (left multicystic kidney and ectopic right kidney), which is actually the diagnosis of LOWE syndrome.

Keywords: lowe syndrome, oculocerebrorenal syndrome, OCRL1 gene, cataract

1. Introduction
The oculocerebrorenal syndrome of Lowe (OCRL), also referred as the Lowe syndrome, is a rare disorder distinguished by a triad of organ system abnormalities, namely ocular disease such as neonatal onset cataracts, mental retardation, and renal dysfunction [1]. It was described in 1952 by Lowe and colleagues [2]. The prevalence of this syndrome has been estimated to occur in 1 out of 500,000 individuals [3]. OCRL results from a mutation in the oculocerebrorenal gene (OCRL1), localized on Xq24-26.1 that encodes a protein highly homologous to inositol polyphosphate 5- phosphatase. This suggests that Lowe syndrome may represent an inborn error of inositol phosphate metabolism [4].
The presence of eye, central nervous system (CNS) and kidney involvement are required for a diagnosis [5]. Congenital bilateral cataract is present at birth in all patients. Other ocular defects include glaucoma and searching nystagmus [6]. Hypotonia and neonatal areflexia are present as well. Motor and mental development are delayed and stereotypic behaviors, such as temper tantrums and aggressiveness, are frequent in adolescence [3]. Moreover, 80% of patients over 18 years-old have seizures [2]. Renal Fanconi syndrome may present in the first months of life, but differ in severity between individuals [7]. Facial dysmorphism is often present and consists of frontal bossing, deep set eyes, chubby cheeks, and a fair complexion [8]. Dental findings include prolonged retention of primary teeth, enlarged pulp chambers, and mildly dysplastic dentin formation [9, 10].

2. Case report
At 2-months-old, a Saudi male infant was the product of a full-term spontaneous vaginal delivery to a 23-year-old woman. Birth weight was 2.1 kg, with normal Apgar scores. He was the first baby of first cousin parents, without a family history of significant diseases. His physical examination after delivery revealed dysmorphic features (frontal bossing, deep seated eyes, depressed nasal bridge) and two cord vessels, while the rest of his physical examination was normal. The baby was initially admitted to the regular nursery, but observed to be hypotonic, for which he was transferred to the neonatal intensive care unit (NICU) for a better assessment. During the NICU admission, he was evaluated by a neonatologist and a geneticist. Laboratory and radiological studies were done, including brain MRI (showing high signal intensity and hypoxic ischemic encephalopathy), renal ultrasound scan (USS) of the kidney (showing left multicystic kidney and ectopic right kidney). Basic laboratory studies (hemoglobin, random blood sugar, and renal function tests) were normal; however, advanced laboratory studies ordered by a geneticist were sent outside of the country. The patient was discharged after 10 days without a clear diagnosis and was given a follow-up appointment for laboratory results.
At 2 months, he was seen in the pediatric clinic of the National Guard Comprehensive Specialized Clinic, Riyadh, Saudi Arabia. His visit was for a routine 2-month vaccination. On physical examination, all growth parameters were below the 5th centile, he was found to have bilateral cataracts, which was not detected in his previous NICU admission; accordingly, he was immediately referred to a pediatric ophthalmologist, after which he was scheduled for cataract extraction surgery, which was done for him after 2 days. The presence of congenital cataracts in this infant (eye problem), in addition, to hypotonia (brain problem), and a multicystic left kidney and ectopic right kidney (renal problems) concluded the diagnosis of Lowe syndrome, which was not achieved by the neonatologist or geneticist previously. The patient was given a new referral to a geneticist, nephrologist, and neurologist with a diagnosis of Lowe syndrome.

3. Discussion
Lowe syndrome is a rare multisystem disorder affecting the eyes, brain, and kidney, and characterized by congenital bilateral cataracts, mental retardation, hypotonia, and renal Fanconi syndrome. Because of the low prevalence of this

disorder (1:200 000 -1:500 000 births) [2, 11], clinicians may not be familiar with it, which is what happened in this case during NICU admission and evaluation by a neonatologist and geneticist. It has a recessive X-linked pattern of inheritance, typically affecting male children, with females acting as carriers. 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 [12]. Congenital cataracts are present at birth in all patients. Glaucoma (present in 50% of patients, with or without buphthalmos) is detected within the first year of life or later. Sight sharpness is compromised, such that aphakia combined with retinal dysfunction, is responsible for nystagmus [6].

In the CNS examination, severe hypotonia [often with the absence of deep tendon reflexes (DTRs)] are present at birth. Motor development is retarded and the autonomous gait becomes apparent generally after the third year. Moderate to severe mental retardation with an IQ of 50 or less is present in 10% of patients. Finally, 87% of patients show evidence of conduct disturbance with auto- and heteroaggressiveness, irritability, outbursts of anger. In addition, 80% of patients over 18 years-old have seizures [2, 3].

Renal disease is primarily characterized by Fanconi syndrome. Severity of renal disease can vary significantly between patients and tends to worsen with age. At birth, many children are asymptomatic. Symptoms generally develop during the first months of life, related to renal bicarbonate, salt, and water wasting, resulting in failure to thrive [7, 13].

At birth, ocular involvement with bilateral cataract and hypotonia may be found in congenital infections (rubella), peroxisomal disorders, mitochondropathies, myotonic dystrophies, or congenital myopathies (Muscle Eye Brain disease). The appearance of renal involvement excludes alternative diagnoses in the first few months of life [3].

Female carriers of Lowe syndrome may be detected in 94% of cases by slit lamp examination; this is because of significant punctate white to the gray opacities and disturbance in the radial fashion of all layers of the lenticular cortex. Antenatal diagnosis is made by enzymatic activity in cultured chorionic villi at 9-11 weeks or in cultured amniotic fluid cells (15-20 weeks) [4].

Management of the disease includes early removal of the cataract to avoid amblyopia. Ocular tone must be tested frequently to diagnose glaucoma. Early targeted rehabilitation is necessary to treat hypotonia, although areflexia does not require treatment. Seizures require treatment with drugs specific to the symptoms. Drugs such as neuroleptics, stimulants, benzodiazepines, antidepressants (tricyclic antidepressants and serotonin reuptake inhibitors) are adequately prescribed but only partially efficacious [2, 3]. Renal tubular acidosis must be recognized and treated promptly with alkali supplements to maintain serum bicarbonate levels at around 20 mEq/L. Potassium citrate is quite useful, as it helps prevent nephrocalcinosis and tends to reduce renal calcium excretion.

4. Conclusion

Lowe syndrome should be suspected in males with congenital cataracts, developmental anomalies, and renal tubular dysfunction of the Fanconi type. Early diagnosis and treatment of metabolic disturbances may delay morbidity and mortality of this syndrome. It is also necessary to emphasize the importance of comprehensive physical exams (including eyes) for all pediatric patients, with special emphasis on newborns.

5. References

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