

# Oculocerebrorenal (Lowe) Syndrome in the Pediatric Orthopaedic Practice: A Review

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## ABSTRACT

The oculocerebrorenal syndrome of Lowe is a rare multisystemic X-linked disorder characterized by the triad of congenital major abnormalities involving the eyes, the nervous system, and the kidneys. This review aims to add a further case in the world literature. The patient was a 12-year-old boy suffering from blindness and rickets. He was referred for hip pain and protective limping on the right side that had appeared a few days ago. The radiographic examination of the pelvis and hips was indicative of Milkman's syndrome of the lateral cortex of the right proximal femur. The diagnostic investigation including pediatric physical examination, laboratory, imaging, and genetic studies led to the diagnosis of the oculocerebrorenal syndrome.

**Key words:** Oculocerebrorenal, Lowe, syndrome, visual impairment, rickets, stress/insufficiency fracture, Milkman/Looser lines.

A variety of primary or secondary diseases may be associated with generalized renal proximal tubule dysfunction. Primary sporadic inherited proximal renal tubular acidosis usually occurs as a component of Fanconi syndrome but may also be due to inherited syndromes, such as cystinosis, galactosemia, and Lowe syndrome. An important form of secondary lesion in children is exposure to ifosfamide that is used in many treatment regimens for Wilms' tumor and other solid tumors.<sup>[1-4]</sup>

The oculocerebrorenal syndrome of Lowe (OCRL) has been primarily described in 1952 as a syndrome characterized by organic aciduria, decreased renal ammonia production, alterations involving the eyes, and mental retardation.<sup>[5-11]</sup>

A recessive X-linked pattern of inheritance due to mutations in the OCRL1 gene has been documented since 1965. The abnormalities seen in Lowe syndrome are thought to be due to abnormal transport of vesicles within the Golgi apparatus. Kidneys show non-specific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.<sup>[12-23]</sup>

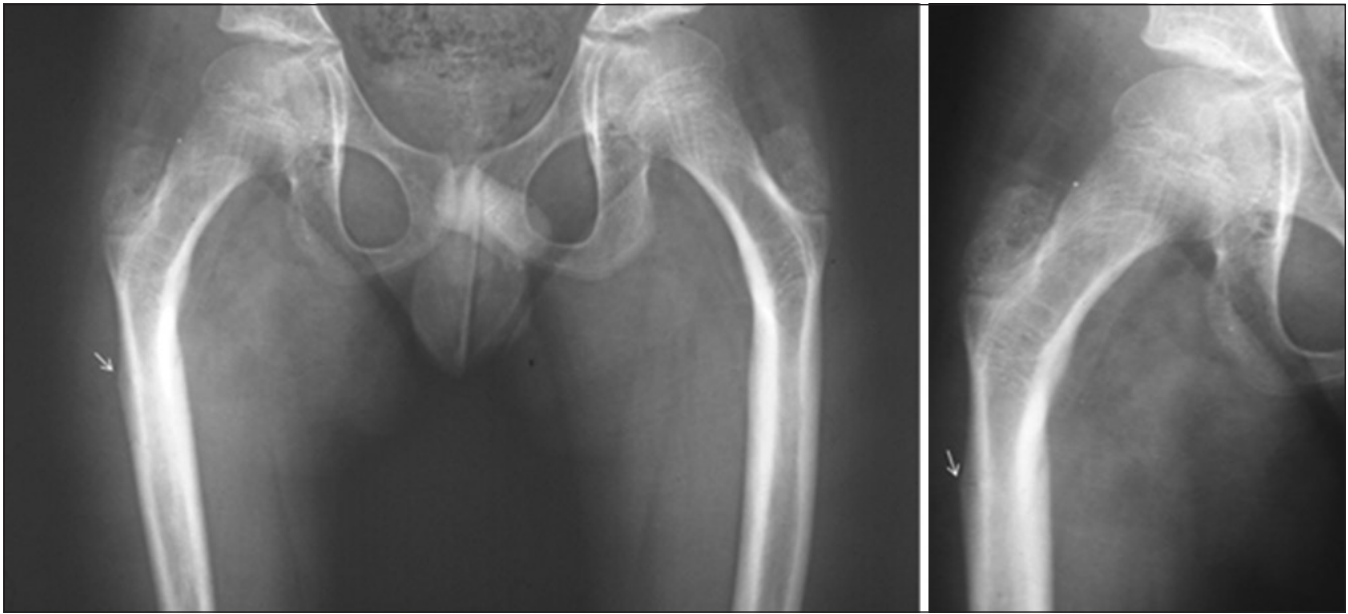
Lowe syndrome is a very rare disease, with an estimated prevalence in the general population of approximately 1 in 500,000 people. Signs and symptoms affecting the eyes, the central nervous system, and the kidneys are required for the diagnosis of Lowe syndrome. Congenital ocular manifestations, usually including bilateral cataract, are present at birth in all patients. Blindness often develops in infancy. Severe muscular hypotonia is also present at birth. It may compromise suction and cause serious respiratory problems in the first period of life. Mental retardation, progressive growth failure, and characteristic behavioral abnormalities are seen in infancy. The manifestations of renal Fanconi syndrome are often recognized in the 1<sup>st</sup> month of life and differ in severity between individuals. The most remote cause of death is the renal tubulopathy, progressively evolving into renal insufficiency. The variability in the clinical and laboratory features of the syndrome probably reflects the number of different mutations of the responsible gene, while it is also consistent with the expectation that one-third of severe X-linked disorders in each generation result from new mutations.<sup>[24-32]</sup>

The generalized proximal tubular dysfunction leads to renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the

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**Figure 1:** A 12-year-old boy was referred for hip pain and protective limping on the right side. Anteroposterior radiograph of the pelvis, hips and proximal femurs showed a Milkman's line of the lateral cortex of the right proximal femur (arrows). There was also bilateral decreased bone density of the femoral necks, thickening of both the proximal femoral and acetabular physal plates, loss of the sharp border of the edge of the proximal femoral metaphysis (fraying), change of the metaphyseal edge from convex to concave (cupping), periosteal reaction with cortical thickening localized to the proximal femoral diaphysis and the ischiopubic ramus, as well as mild coxa valga.

proximal tubule. The most clinically relevant consequences are hypophosphatemia due to phosphate losses and proximal renal tubular acidosis due to bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution.<sup>[4,33-35]</sup>

Skeletal muscle alterations, such as hypotonia, areflexia, and joint hypermobility, as well as weight and height deficits may occur as a consequence of tubular alterations. Tenosynovitis, joint effusions, and contractures have also been reported. Severe orthopaedic deformities may occasionally be encountered, such as subluxed or dislocated hips, scoliosis, kyphosis, cervical abnormalities, and rickets. Renal rickets and osteomalacia due to renal dysfunction may lead to bone pain, limited range of motion, and pathological fractures.<sup>[36-43]</sup>

Rickets is also known as rachitis. It refers to osteomalacia in the pediatric population, occurring before the closure of the physal plates. Rachitic radiographic changes are due to insufficient conversion of osteoid matrix to mineralized bone at the level of the growth plates and shafts. The former results in thickening of the growth plate, growth retardation, and delayed skeletal development. The latter is caused by calcification of the unmineralized osteoid that elevated the periosteum. The physal changes are most prominent in rapidly growing growth plates and are easily visualized on the posteroanterior radiographs of the wrist and knee joints. The edge of the metaphysis

loses its sharp border, which is described as fraying. The edge of the metaphysis also changes from a convex or flat surface to a more concave one, which is termed cupping. There is a widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Physal margin irregularity of the metaphysis is also evident. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Various skeletal deformities as well as insufficiency fractures may occur in children with advanced rickets.

Skeletal deformities may be evident in the skull (delayed closure of anterior fontanelle, frontal bossing, and craniotabes), chest (rachitic rosary, Harrison's sulcus or groove, and pigeon chest deformity), spine (scoliosis, kyphosis, and lordosis), and the long bones. The latter are usually localized to the knees (genu varum or valgus) and hips (coxa vara predisposes to femoral neck insufficiency fractures, while coxa valga may be secondary to reduced muscle tone and ambulation).<sup>[4,44-61]</sup>

Stress fractures are divided into insufficiency and fatigue fractures, and they are generally classified in compression and tension lesions. While fatigue fractures occur in normal bone following repetitive excessive activity, insufficiency fractures occur in weak bone under normal loading. Insufficiency injuries are also termed Milkman's syndrome or pseudofractures, Looser's lines or zones, and

spontaneous fractures. They are most commonly due to rickets or osteomalacia. They are oriented at right angles to the long axis of the involved bone, they do not cross the entire bone, they involve the whole skeleton and they are usually localized symmetrically on the concave side of the bone (compressive lesions). They may also rarely occur in Paget's disease, hyperparathyroidism, renal osteodystrophy, osteogenesis imperfecta, fibrous dysplasia, and X-linked hypophosphatemia with Vitamin D-resistant rickets.<sup>[62-75]</sup>

A 12-year-old boy was seen in the orthopaedic emergency department for protective limping on the right side, consecutive to right lateral thigh aching pain that had appeared a few days ago. The child was accompanied by an officer of the "school centre for visually impaired children". No specific history of a traumatic injury was reported. Joint examination of the hips and knees was normal. There was an area of severe tenderness on palpation that was localized distally to the right greater trochanter.

A long medical history of eye and renal abnormalities was given. The former included cataract of both eyes and bilateral glaucoma, which was complicated by blindness a few years ago, while the latter included proximal renal tubular dysfunction of the Fanconi type. Intellectual disability and walking difficulties were also reported.

The radiographic examination of the hips was indicative of a radiolucent line of the proximal aspect of the right femur that was oriented perpendicular to the lateral femoral cortex. In addition, coarsening of the trabecular pattern of the proximal femur, widened epiphyseal plates of both the proximal femoral and acetabular physeal plates, periosteal reaction of the proximal femoral diaphysis and ischiopubic ramus, and mild coxa valga (135°) were bilaterally diagnosed (Figure 1).

Walking with crutches was the only provided treatment to support and protect the right lower limb from a complete fracture until complete resolution of the clinical symptoms and signs. The child was referred to the pediatric department for further evaluation and proper syndrome diagnosis.

Laboratory tests revealed hypocalcemia, bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, and an increased serum alkaline phosphatase activity. Further studies showed sodium and potassium wasting as well as aminoaciduria and proteinuria. Based on both clinical and biological data, Lowe syndrome was suggested. Molecular genetics analysis secured the diagnosis.

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