Ricketsial Findings: Presenting As Features of Oculocerebrorenal Syndrome (Lowe Syndrome): Case Report

Rikets Bulguları: Oküloserebrorenal Sendromun Özellikleri Olarak Bulgu Veren

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ABSTRACT Oculocerebrorenal syndrome of Lowe is an X-linked recessive disorder that predominantly affects males and characterized by growth and mental retardation, congenital catharact and renal tubular dysfunction. The responsible gene locus product plays a role in Golgi vesicular transport. A 6-years-old boy with bilateral congenital cataracts, radiological and examination findings of rickets and developmental delay was presented. Radiography showed the typical radiological findings of rickets; the distal ends of upper and lower limbs were widered, concave and frayed. Also T1-weighted magnetic resonance images were showed hypointense lesions while the proton magnetic resonance spectroscopy revealed a myoinositol peak at 3.56 ppm suggesting the presence of gliosis on bilateral subcortical white matter. Rickets accompanied to Lowe syndrome is rarely reported in the literature.

Key Words: Rickets; renal osteodystrophy; oculocerebrorenal syndrome

ÖZET Lowe'un oküloserebrorenal sendromu; X'e bağlı resesif geçişli, büyüme geriliği, mental retardasyon, konjenital katarakt ve tübüler disfonksiyon ile karakterize olup, daha çok erkekleri etkilemektedir. Sorumlu tutulan genin sentezi Golgi veziküler transportunda görev almaktadır. Çalışmada, iki taraflı konjenital kataraktı olan, radyolojik ve fizik muayene bulguları ile gelişme geriliği ve rikets tespit edilen 6 yaşında bir erkek hasta sunulmuştur. Radyografide, riketsin tipik bulguları olan alt ve üst ekstremitelerin distal uçlarında genişleme, konkavlaşma ve fırçalanmalar görülmüştür. Ayrıca, T1 ağırlıklı manyetik rezonans görüntülemede hipointens lezyonlar ve proton manyetik rezonans spektroskopide çift taraflı subkortikal beyaz maddede gliozisi destekleyen 3.56 ppm'de miyoinositol piki görülmüştür. Riketsin eşlik ettiği Lowe sendromu olguları literatürde nadiren bildirilmiştir.

Anahtar Kelimeler: Rikets; renal findings; oküloserebrorenal sendrom

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Oculocerebrorenal syndrome, also known as Lowe syndrome, is an X-linked recessive disorder which first reported by Lowe et al in 1952.[1] Primary clinical manifestations include congenital catharact, mental retardation and renal tubular dysfunction (Fanconi syndrome). The severity of the renal disease can vary between patients and most of them are asymptomatic at birth. Renal disease can also lead to the development of rickets. Reported prevalence is only a few cases per 100.000-500.000 births.[2,3] The responsible gene, located at Xq26.1m, is

called OCRL1 and it encodes a phosphatidylinositol-4, 5-biphosphate-5 phosphatase that is found in Golgi complex.[3] A mutation in the OCRL1 gene locus causes this syndrome by a reduction of the OCRL1 protein. We report, a 6-years-old boy with the clinical features of Lowe syndrome who has distinct radiological and examination findings of rickets. Our purpose is to check out clinical features of Lowe syndrome that was presented with rickets and emphasize the diagnostic importance of proton magnetic resonance spectroscopy.

CASE REPORT

A 6-years-old boy was admitted to our hospital suffering from difficulty in walking for six months. He was a term baby and borned by spontaneous vaginal way with a birth weight of 2950 g and bilateral congenital catharacts. The perinatal history was unremarkable but he had motor developmental delay and any seizures were not observed. He was not given vitamin D or multivitamin combinations during infancy and then. Family history revealed that he was born out of a consanguineous marriage and has three brothers who were in good health.

His height was 105 cm (< 3 p, -2.6 SDS), weight was 13 kg (< 3 p, -4.4 SDS) and occipital front circumference was 47.5 cm (< 3 p, -2.4 SDS). Frontal bossing, small nose, deep-set eyes, normally placed large ears, elevated palate, bilateral cataracts, multiple deformed tooth in the mouth, 'O bines' deformity with rachitic rosaries were examination findings. He was using eyeglasses. Other examination findings were all normal. Laboratory assessment revealed; hypercalcaeuria (urine calcium concentration was ≥ 4 mg/kg/day), hypokaliemia (2.4 mEq/L, normal ranges were 3.6-5.1) hyponatremia (125.9 mEq/L, normal ranges were 136-144) and metabolic acidosis (pH: 7.29; PCO_2: 30.1; HCO_3: 10.1 mmol/L and base excess: 7.6 mmol/L). Serum calcium, phosphorus, alkaline phosphatase and parathormone levels were; 9.2 mg/dL (normal ranges 8.9-10.3), 2.9 mg/dL (normal ranges 3.7-4.7), 354 u/L (normal ranges 0-500) and 31 pg/mL (normal ranges 8-76), respectively and all values controlled tree months consecutively. There was no glucosuria, however proteinurea (19 mg/m^2/hour) was significant. Also tubular reabsorption of phosphorus was 82% (normal range %93 <), urine Ca/Cr, PO_4/Cr were 0,65 (normal ranges 0.04-0.8) and 1.02 (normal ranges 1.2-5) respectively. Other biochemical and hormonal analyses were normal. Renal ultrasonography (USG) demonstrated micro calcules in the renal parenchyma. On radiography; the epiphyses of radius and ulna appeared widered, concave and frayed (Figure 1a, b). Nevertheless a spontaneous fracture was determinated on the right knee. Bilateral subcortical cystic lesions were detected on cranial magnetic resonance images (MRI) and proton magnetic resonance spectroscopy of subcortical white matter showed a myoinositol peak at 3.56 ppm suggesting the presence of gliosis (Figure 2a, b). He was treated with oral administration of 0.5 μg/day calcitriol. Also alkaline supplementation including sodium, potassium citrate and sodium bicarbonate were added on the therapy. Because of the decreased serum phosphorus levels

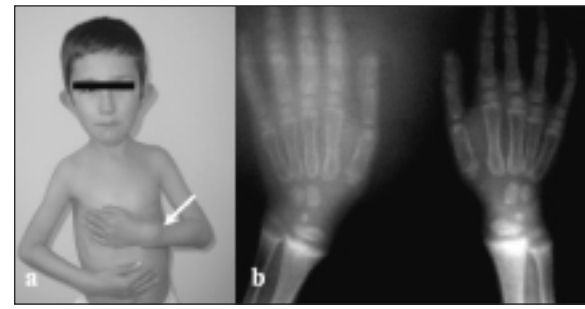

FIGURE 1: (a) The expension of the wrists due to rickets,(b) Bilateral widered, concave and frayed epiphyses of radius and ulna on radiography.

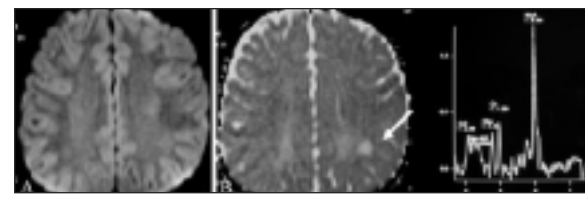

FIGURE 2: (a) Normal signal on b= 1000 s/mm^2 and, (b) high ADC (apparent diffusion coefficient) values on subcortical white matter on diffusion magnetic resonance imaging, (b) Moderate myoinositol peak on proton magnetic resonance spectroscopy at 3.56 ppm.

and tubular reabsorption of phosphorus, replacement treatment was given. On follow up, his difficulty in walking recovered in 6 months and all laboratory parameters of urine and serum became to normal.

DISCUSSION

The clinical diagnosis of Lowe syndrome is based on specific ophthalmologic, nurologic and renal abnormalities.[4] Our patient is diagnosed as Lowe syndrome based on clinical and laboratory findings.

Essentially, renal findings of Lowe syndrome vary between patients and the severity of renal disease changes from asymptomatic to chronic renal failure. Metabolic acidosis due to proximal tubular bicarbonate wasting and hypophosphatemia due to renal phosphate wasting can be related with poor growth. Otherwise renal phosphate wasting is associated with renal rickets, osteomalacia and pathological fractures. In addition to the commonly seen tubular dysfunction, several glomerular changes have been recognized such as glomerular sclerosis, thickening of basement membranes and fusion of the foot processes.[3] Recently, increased urine retinol binding protein and N-acetyl-glucosaminidase have been used for detecting early proximal tubular dysfunction in Lowe syndrome.[5]

While admitting to our clinic the primer complaint of our case was difficulty in walking which might be a rachitic symptom. Also clinical examination revealed the rachitic findings such as 'O bines' deformity and rachitic rosaries. Yet, the reason that reminded us to research detailed was bilateral congenital cataract which was accompanied to ricketsial findings. Signs of rickets were showed radiologically also with the normal serum parathormone, calcium and decreased phosphate levels. However hypercalcaeuria, proteinurea were significant and tubular reabsorption of phosphorus was decreased. Renal calcule formations were detected on ultrasonography. It could be related with hypercalcaeuria and metabolic acidosis. Also hypercalcaeuria, phosphorurea and metabolic acidosis were all caused rickets together in our patient. It is known that the severity of renal disease changes from asymptomatic to Fanconi syndrome. So, urine and blood analysis of the case showed the laboratory findings of Fanconi syndrome.

Cataract is the major finding of all clinical features as in our patient. It develops in utero and is caused by altered migration of the crystalline embryonic epithelium.[6] Nystagmus, corneal and conjunctival cheloids are the other eye associated findings.[7] Also, incomplete lenticular opacities were reported.[8] Our case had bilateral catharact and was not operated before.

Unfortunately nervous system is affected in the disease. Hypotonia is usually present at birth and suctioning problems may occur. Mental problems are not usual but about 10% of patients show slight mental retardation with an IQ of 50 or less.[3] Also, cognitive impairment, behavioral disturbances, motor milestone delay, areflexia and seizures can be observed.[9] In the present patient there was not any neurological symptoms or signs except the hypotonia at birth and motor developmental delay later on. Electromyogram and motor and sensitive velocity are normal in these patients. On cranial MRI; ventriculomegaly, periventricular cysts that the intensities vary between T1 and T2-weighted images and focal or diffuse myelin pallor can be showed. But, prominent myoinositol peaks suggesting the presence of gliosis on proton magnetic resonance spectroscopy at 3.56 ppm is typical. Also on diffusion MRI normal signal on b= 1000 s/mm^2 and high apparent diffusion coefficient (ADC) values have been gained.[10] However these lesions were not correlated with the severity of clinical manifestations.[11]

Proton magnetic resonance spectroscopy is a very promising technique that provides in vivo biochemical information on a variety of brain compounds. Also spectroscopy can be used to monitor the effectiveness of therapy for metabolic disorders.[12] In different diseases a variety of representative resonances are detected, for example; N-acetylyaspartate peak at 2 ppm in adrenoleukodystrophy, myo inositol peak at 3.56 ppm in Lo-

we syndrome and lactate peak at 1.33 ppm in mitochondrial diseases.

In the present case MRI showed hypointense lesions on T1- weighted images in the bilateral subcortical white matter while the lesions appeared hyperintense on T2-weighted images. The proton spectroscopic study of the subcortical white matter showed a myo inositol peak at 3.56 ppm suggesting the presence of gliosis (Figure 2a, b).

In conclusion; Lowe syndrome is typically diagnosed with clinical and laboratory findings in our case. Also, rarely rickets can be occured as a companent of Fanconi syndrome in these patients.

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