A Case of Rhizomelic Chondrodysplasia Punctata, Type I

Rizomelik Kondrodisplazi Punktata Tip 1

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ABSTRACT The aim of this report is to describe a case of rhizomelic chondrodysplasia punctata (RCDP) and discuss differential diagnosis of this rare condition from other chondrodysplasias. A 12-day old male infant whose all anthropometric measurements were below the 10th percentile presented with respiratory distress. His physical examination revealed that rhizomelic micromelia, joint contractures, pes equinovarus deformity and bilateral cataracts, and systolic heart murmur. Roentgenogram demonstrated short humerus and femur, punctate calcifications and abnormal ossification in metaphyses and epiphysis. Additionally secundum ASD and PDA were determined on echocardiography. The diagnosis of RCDP is based on clinical findings and confirmed by clinically available biochemical test. RCDP is a rare multisystem peroxisomal disorder. Diagnosis is usually based on clinical and radiological criterias, however three biochemical tests of peroxisome function are used to confirm the diagnosis of RCDP, red blood cell concentration of plas-malogenes, plasma concentration of phytanic acid and plasma concentration of very long chain fatty acid.

Key Words: Chondrodysplasia punctata, rhizomelic, phytanic acid, peroxisomes

ÖZET Bu çalışmada Rizomelik Kondrodisplazi Punktata (RKDP) olan bir olgu sunularak diğer kondrodisplaziler ile ayrıcı tanı yapılmıştır. Tüm antropometrik ölçümleri 10.persantilin altında olan 12 günlük erkek hasta solunum sıkıntısı nedeni ile kliniğimize başvurdu. Fizik muayenesinde rizomelik mikromeli, eklemlerde kontraktürler, pes ekinovarus deformitesi, bilateral katarakt ve sistolik üfürüm saptandı. Radyolojik incelemede humerus ve femur kısa görünümde olup metafiz ve epifizlerde punktat kalsifikasyonlar görüldü. Ekokardiyografik incelemesinde ASD ve PDA tespit edildi. Klinik, radyolojik ve laboratuvar tetkikleri sonucunda hastaya RKDP tanısı konuldu. RKDP nadir görülen multisistemik peroksizomal hastalıklardan olup tanı klinik bulgular ile konulmaktadır. Eritrosit plazmolojen düzeyleri, plazma fitanik düzeyleri ve plazma uzun zincirli asit düzeyleri gibi peroksizomal fonksiyonlar RKDP tanısının biyokimyasal belirteçleridir.

Anahtar Kelimeler: Rizomelik kondrodisplazi punktata, fitanik asit, peroksizom

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Chondrodysplasia punctata (CDP) represents heterogeneous group of disorders; X-linked dominant form (Conradi-Hunnerman disease), X-linked recessive CDP, autosomal dominant CDP and rhizomelic CDP and many other milder forms have been described. Among these, rhizomelic chondrodysplasia punctata (RCDP) is a rare multisystem developmental disorder. It was demonstrated that RCDP is a form of peroxisome biogenesis disorders (PBDs).[1] Similar biochemical abnormalities were also

defined as in other PBDs such as Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. RCDP patients have subnormal levels of red cell plasmologens and progressive accumulation of phytanic acid starting from normal at birth. Characteristic findings of this disorder are the presence of punctate calcifications of the cartilage, contractures of joints, vertebral clefts, cataracts, a characteristic facial appearance, severe growth deficiency and mental retardation. Other findings which were reported in variable frequency, are ichthyosis, suction and feeding difficulties, congenital heart defects, alopecia, hearing loss, visual impairment, convulsions, kyphoscoliosis and spina bifida. Prognosis of RCDP is poor with recurrent pulmonary infections and survival beyond 1 year is rare.

The combination of punctate calcifications, rhizomelia and the biochemical abnormalities (deficient red cell plasmalogens and accumulation of phytanic acid) is pathognomic for RCDP. By presenting this case report we aimed to discuss the differential diagnosis of RCDP.

CASE REPORT

A 12-day old male infant was referred to our hospital with abnormal shape of the body and respiratory distress. He was born at term weighing 1560 g as a second child of non-consanguineous 25-year-old mother and 30-year-old father. His mother had nor history of prenatal regular doctor visit neither prenatal ultrasonography. Detailed family history is non remarkable for skeletal dysplasia or congenital anomalies. On admission all anthropometric measurements were below the 10th percentile with a weight of 1450 g, height 38 cm, head circumference 29 cm. Physical examination revealed rhizomelic micromelia in which shortness of humerus and femur are most prominent, joint contractures, kyphosis, bilateral pes equinovarus deformity and bilateral cataracts, hypoplasia of external right ear channel, broad nasal bridge, micrognathia, bulbous point of the nose, long filtrum, and second degree systolic heart murmur (Figure 1). In laboratory investigation complete blood count, serum glucose, calcium, phosphorus, blood urea nitrogen, electrolytes, AST, ALT, alkaline phosphates were all within the normal range. Plasma phytanic acid level at two months of age was 41.13 mcg/ml (normal levels 0.42-3.77). Chest roentgenogram showed short humerus, punctate calcifications and abnormal ossification in metaphyses and epiphysis and infiltrates in lung parenchyma (Figure 2). Vertebral X-ray showed kyphosis and vertebral clefts (Figure 3). Opthalmological examination was completely normal. Echocardiography revealed secundum ASD and PDA. USG of the abdomen was normal. Temporal CT for the evaluation of internal ear was normal. Cerebral MR showed normal myelinization, asymmetry in ventricular system. Progressive respiratory distress necessitated mechanical ventilation. At first ten days of mechanical ventilation, he received only total parenteral nut-

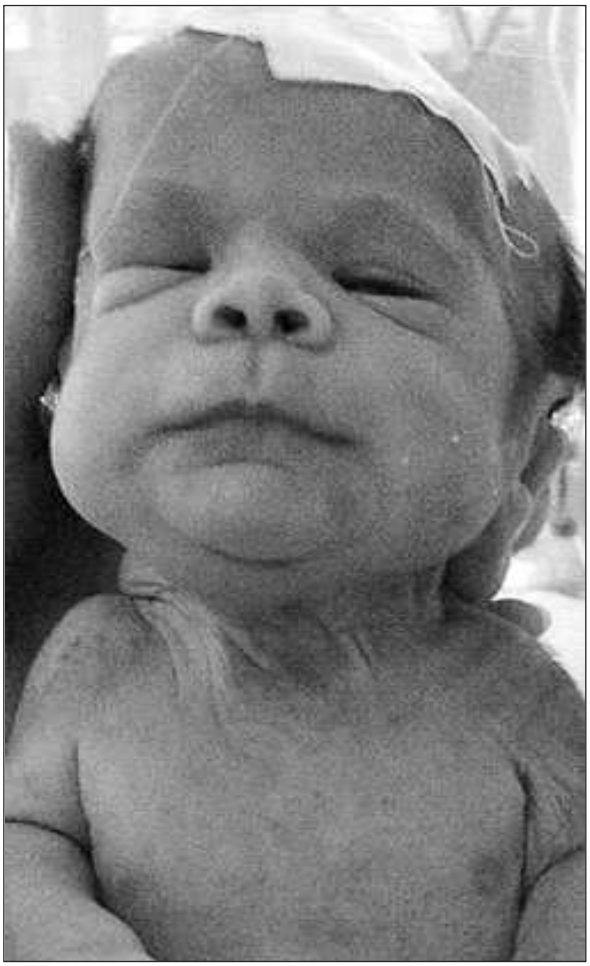

FIGURE 1: Typical facial appearance of case.

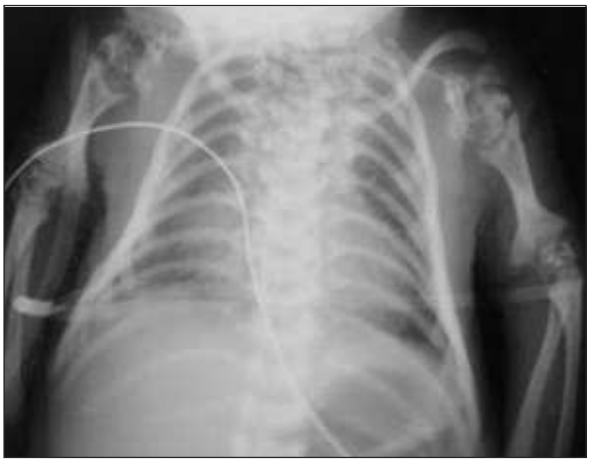

FIGURE 2: Roentgenogram showed short humerus, punctate calcifications and abnormal ossification in metaphyses and epiphysis and infiltrates in lung paranchyme.

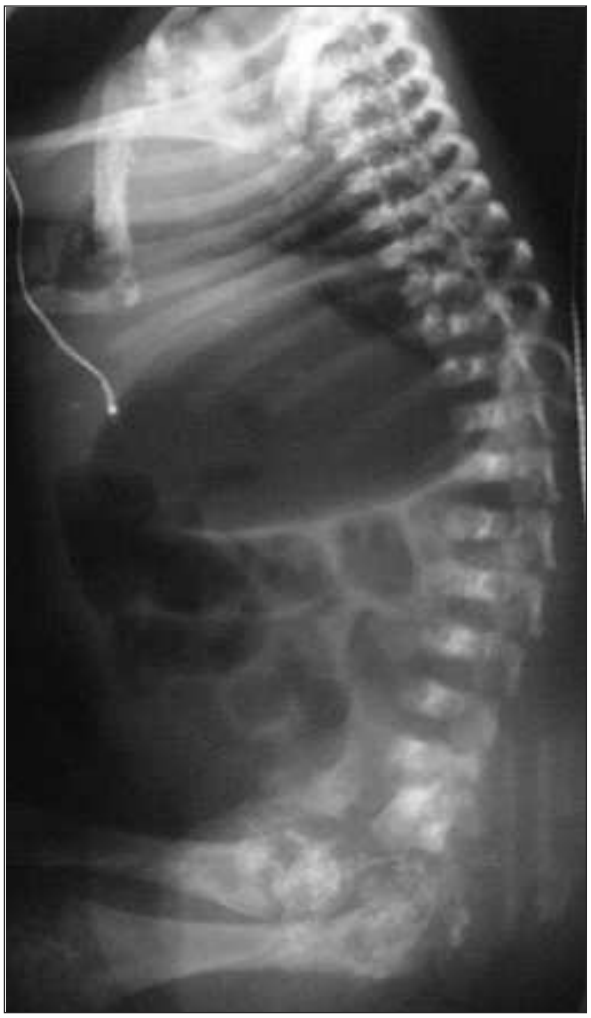

FIGURE 3: Roentgenogram showed kyphosis and vertebral clefts.

rition because of respiratory distress. Parenteral feeding with gavage feeding including formula, were started consecutively on 11th days of his admission he was followed-up with mechanical ventilation with continuous positive airway pressure (CPAP) mode. He received formula as gavage feeding during two months. On 78th day of his admission, he required mechanical ventilation and total parenteral nutrition re-started after stopping gavage feeding because of deteriorated clinical status. He died of respiratory failure after 70 days of hospitalization.

DISCUSSION

Rhizomelic chondrodysplasia punctata (MIM 215100) is a rare peroxisomal disorder. Four peroxisomal abnormalities have been identified in the classic form of RCDP: deficiency of dihydroxyacetonephosphate acyltransferase (DHAPAT) and alkyl-DHAP synthase, deficient phytanic acid alpha-oxidation, and an abnormal molecular form of peroxisomal thiolase.[2,3] Patients showing all the clinical and typical radiologic features of RCDP in varying degrees, but lacking the tetrad of biochemical abnormalities found in classic RCDP patients were identified. In these patients isolated deficiencies of alkyl-DHAP synthase and dihydroxyacetonephosphate acyltransferase were found. They are grouped as Type II and type III RCDP.[4] There are other disorders with similar punctate cartilaginous changes such as X-linked chondrodysplasia punctata, multipl forms of Zellweger syndrome, maternal ingestion of certain anticoagulants (dicoumarol or warfarin) in early pregnancy and occasional forms of trisomy 18. Thus, care must be taken in diagnosing an infant or child presenting with punctate calcifications. The combination of punctate calcifications, rhizomelia, and the biochemical abnormalities (deficient red cell plasmalogens and accumulation of phytanic acid) are pathognomic for RCDP.

Although, in RCDP patient's broad nasal bridge, micrognathia, bulbous point of the nose are described as features giving the face's characteristic appearance, none of them are so prominent to allow physician to notice of first glance. Cataracts are

present in about 72% of the cases and ocular phenotype is helpful for the differential diagnosis of RCDP. Happle[5] suggested that cataracts are consistently absent in the autosomal dominant form of chondrodysplasia punctata and present in about two-thirds of the rhizomelic and X-linked dominant forms. In the rhizomelic form, the opacities tend to be bilateral and symmetric. However in the X-linked form these opacities are usually asymmetric and often unilateral. In our patient cataracts were detected bilaterally.

Joint contractures were described almost all of the cases. Bilateral shortening and metaphyseal widening of the humerus and femur, punctate calcification of the epiphysis and coronal clefts are typical and were present in our patient. The punctate lesions result from the degeneration of cartilage, represented by chondrocytes with picnotic nuclei and eosinophilic cytoplasm, followed by ossification. Coronal cleft of the vertebral bodies represent embryonic arrest with cartilage occupying the cleft between the anterior and posterior parts of the vertebral bodies. Some cases had kyphoscoliosis while our patient had kyphosis. Cardiac defects are reported rarely such as pulmonary stenosis and ASD, VSD.[6] Our case had ASD and PDA. Ichthyosis-skin changes-alopecia was described as 27% was not found in our case.

Severe mental retardation, microcephaly, convulsions, hearing loss, visual impairment is the neurologic features. Routine brain imaging is either normal or has shown cerebral and cerebellar atrophy with enlargement of the ventricles and CSF spaces and sometimes increased signal intensity in the periventricular white matter and centrum semiovale, delayed myelinization. Since it is not always possible to demonstrate white matter abnormalities in MRI studies, multivoxel magnetic resonance spectroscopy is recommended.[7] Multivoxel magnetic resonance spectroscopy showed reduced choline peak in the white matter in the case of normal myelinization in MRI.

A RCDP is a distinct PBD phenotype and in nearly all instances results from mutations in the PEX7 gene, which encodes peroxin-7, the PTS2 receptor.[8] More than twenty mutations which result in peroxisome abnormalities, have been described. We could not perform molecular genetic tests in our patient. Biochemically RCDP patients have subnormal levels of red cell plasmologens and progressive accumulation of phytanic acid starting from normal at birth and increasing to levels more than 10 times normal by age one. Phytanic acid level of our patient was nearly 10 times of normal value by age two months. We could not perform red blood cell concentration of plasmalogenes and plasma concentration of very long chain fatty acid.

Survival beyond 1 year of age is rare among RCDP patients and death usually occurs due to respiratory complications as in this case. Recently, White et al.[9] reported 90% survival at one year of age, 50% survival to age six years, and approximately 20% survival at age 12 years. Differential diagnosis of RCDP is important to provide management of the patient and education of the parents about this severe healthy problem.

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