GAVIN PUBLISHERS

OPEN ACCESS

Archives of Surgery and Clinical Case Reports

Demirtaş F, et al. Arch Surg Clin Case Rep 3: 147.

DOI: 10.29011/2689-0526.100147

Case Report

A Dysmorphic Neonate with Secondary Hyperparathyroidism and Severe Skeletal Demineralization: I-Cell Disease

Ferhan Demirtaş*, Atasay B, Craja E, Ozsu E, Okulu E, Eminoglu FT, Erdeve O, Şıklar Z, Arsan S

Faculty of Medicine, Ankara University, Turkey

***Corresponding author:** Ferhan Demirtaş, Faculty of Medicine, Ankara University, Turkey

Citation: Demirtaş F, Atasay B, Craja E, Ozsu E, Okulu E, et al. (2020) A Dysmorphic Neonate with Secondary Hyperparathyroidism and Severe Skeletal Demineralization: I-Cell Disease. Arch Surg Clin Case Rep 3: 147. DOI: 10.29011/2689-0526.100147

Received Date: 16 September, 2020; **Accepted Date:** 21 September, 2020; **Published Date:** 28 September, 2020

Abstract

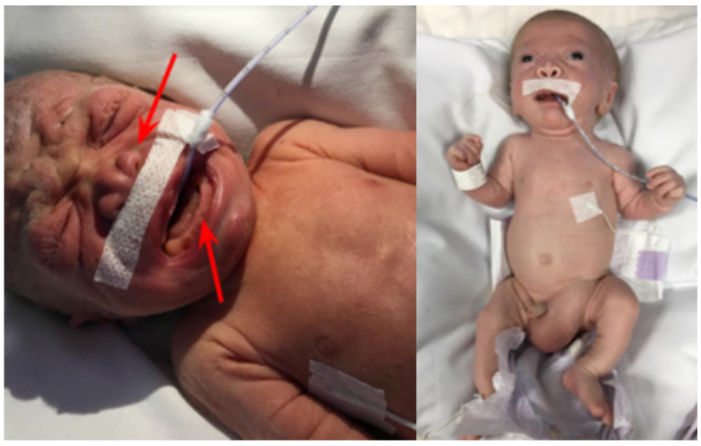
Mucolipidos type 2 (I- cell) is a rare lysosomal storage disease with autosomal recessive inheritance caused by deficiency of N-acetylglucosamine-1-phosphotransferase. It presents with dysmorphological features such as atypical facial appearance, skeletal anomalies and biochemical and radiological evidence of abnormal bone mineralization. We present a newborn infant having dysmorphological features and signs of secondary hyperparatiroidism with the diagnosis of mucolipidos type 2.

Introduction

Secondary hyperparathyroidism results from maternal hypocalcemia or failure of active calcium transport across the placenta results in hypocalcemia and subsequent parathyroid hormone production in the fetus. Skeletal demineralization findings such as short extremities, metaphyseal enlargement and irregularity in the distal part of long bones, tubulation disorders of bones, kyphoscoliosis can be seen as a result. Mucolipidos type 2 (I- cell), one of the causes of secondary hyperparathyroidism, is a rare lysosomal storage disease, presenting with dysmorphological features such as atypical facial appearance, skeletal anomalies, bone mineralization defects and connective tissue disorders. It has clinical, biochemical and radiological characteristics of both endocrine and metabolic diseases. We present a newborn infant having typical facial and skeletal anomalies and signs of secondary hyperparatiroidism with the diagnosis of mucolipidos type 2.

Case

A newborn baby with atypical appearance was admitted to the neonatal intensive care unit because of respiratory distress. He was born at 36 weeks and 4 days' gestation by caesarean section to a 23-year-old healthy Turkish woman as the second pregnancy. His birth weight was 1570 g, and the apgar scores were 5 and 8 at 1 minute and 5 minutes respectively. There was no consanguinity between the parents. Physical examination revealed tachypnea and subcostal retractions, symmetrical growth retardation with body weight of 1570 g (<3p), length of 34 cm (<3p), head circumference of 27 cm (<3p), and atypical facial appearance with narrow forehead, puffy eyelids, wide orbits, open (anteverted) nostril, gingival hyperplasia, large tongue and skeletal anomalies with short extremities and bending of extremities with enlargement of the bone in the distal radius of the ankles and distal tibia and fibula of the ankles with palpation (Picture 1) (Table 1). He received respiratory support with nasal BPAP.



Picture 1: The patient's atypical facial appearance, ingiunal hernia and deformities in the extremities.

Symmetrical growth retardation
Atypical facial appearance:
Narrow forehead, puffy cheeks, puffy eyelids, wide orbits, hypoplasic nose, open (anteverted) nostril, flat nose bridge, long philtrum, gingival hyperplasia, large tongue
Limb anomalies:
Short extremities; bilateral forearms in pronation Bending of the extremities Enlargement of the bone in the distal radius of the ankles with palpation Enlargement of the bone in the distal tibia and fibula of the ankles with palpation
Inguinal hernia, hydrocele

Table 1: Dysmorphic findings.

Laboratory evaluation revealed extremely high Parathyroid Hormone (PTH) 221,9 pg/ml (N:17-42) and low 25-Hydroxyvitamin D (25(OH)D) 9,6 ng/ml (N>20) level with normocalcemia 9.3 mg/dl (N:9.0-11.0), normal phosphate 4.12 mg/dl (N:4.0-8.0) and very high Alkaline Phosphatase (ALP) 1339 U/L (N:48-406) (Table 2). He had combined conjugated and unconjugated hyperbilirubinemia that responded to 10 mg ursodeoxycholic acid three times a day. Renal function was normal. Investigation of the mother showed normal calcium, phosphate, PTH and vitamin D levels. The mother used alcohol and other substances at the beginning of the pregnancy. Babygram of the patient revealed short extremities, prominent metaphyseal enlargement and irregularity in the distal of both radius-ulna and tibia-fibula, tubulation disorder in femur, punctuation in talus, thoracic scoliosis, spikes in iliac bone, elongation in pelvis (Figure 1).

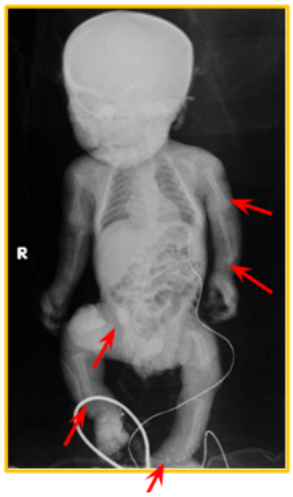


Figure 1: Babygram of the patient.

The patient was treated with 1200 U/day of vitaminD3 and calcium carbonate. Further increament of ALP (ALP: 2635 U / L) and decreament in PTH level (PTH: 192 pg / ml) was relevant with increased osteoblastic activity at the beginning of the treatment. The PTH level was decreased to 118 pg/ml in 4 weeks (Table 2).

	Ca (9-11 mg/dl)	P (4-8 mg/dl)	ALP (48-406 U/L)	PTH (17-42 pg/ml)	25(OH)D (>20 ng/ml)
Admission	8,9 mg/dl	4,1 mg/dl	936 U/L		
1st week	9,3 mg/dl	4,12 mg/dl	1339 U/L	221,9 pg/ml	9,66 ng/ml
1200 U/day 25 (OH)D-1st week	9,3 mg/dl	4,12 mg/dl	2635 U/L	192 pg/ml	9,7 ng/ml
1st month	9,8 mg/dl	4,9 mg/dl	1904 U/L	118 pg/ml	45,6 ng/ml

Table 2: The follow up of patient's laboratory values.

Biochemical and radiological evidence of abnormal bone mineralization accompanying typical dysmorphic findings made us think of lysosomal storage diseases associated with skeletal dysplasia (dyzostosis multiplex group), mucolipidosis type 2 (I-cell). Plasma enzyme studies showed elevated activities of multiple serum enzymes; α -mannosidase 4898 µmol/l/h (20-100), total-hexominidase 42.618 µmol/l/h (600-3.500) and arylsulfatase 5241 µmol/l/h (150-500). These laboratory findings confirmed the diagnosis of mucolipidosis type 2. Homozygous mutation on GNPTAB gene NM_024312.5 c.3091 C> T (p.R1031*) (p.Arg1031Ter) also supported the diagnosis. The patient diagnosed in the early neonatal period and was discharged on the 45th day of life. On follow-up, the baby was deceased due to aspiration. Information and pictures of patient were used with the approval of family.

Discussion

Mucolipidosis type 2 is a lysosomal storage disease with autosomal recessive inheritance with frequency of approximately 1 in 640.000 live births [1]. This lysosomal storage disease is caused by deficiency of N-acetylglucosamine-1-phosphotransferase leading elevated lysosomal hydrolases in the plasma and body fluids of affected individuals due to failure of targeting enzymes (lysosomal acid hydrolases) to the lysosomes [2]. The marker, identified as a mannose-6 phosphate residue on the lysosomal enzyme, triggers endocytosis into the lysosome. Mannose-6 phosphate deficient enzymes can not reach lysosome and they form vacuoles or inclusions in the cell [3-5]. Mucolipidosis type 2, also called I-cell (inclusion cell) disease, is characterized by the presence of intracytoplasmic inclusions in cells of mesenchymal origin, especially fibroblasts [2]. In mucolipidosis type 2, skeletal anomalies; bone and cartilage structure abnormalities and heart, kidney, liver problems can be observed and patients are often diagnosed at 6-12 months of age [2,6].

The age of onset, tissue and organ involvement and radiological findings are variable. Intrauterine growth retardation, low birth weight, atypical facial appearance such as narrow forehead, plumpy cheeks, puffy eyelids, anteverted nostril, gingival hyperplasia, large tongue and skeletal anomalies such as flexed positioned extremities, kyphoscoliosis, new bone formations on tubular bones and inguinal hernia as connective tissue disoerders can be present. Our patient has intrauterine growth retardation, low birth weight, atypical facial appearance findings and skeletal anomalies of I-cell disease. Secondary hyperparathyroidism is characterised by increased Parathyroid Hormone (PTH) in response to hypocalcemia. Maternal hypocalcemia or failure of active calcium transport across the placenta results in fetal hypocalcemia and PTH surge. Intra uterine onset hyperparathyroidism may lead skeletal demineralization findings such as short extremities, enlargement in the distal of long bones, kyphoscoliosis.

ALP and PTH elevation with normocalcemia and abnormal bone mineralization findings such as enlargement and irregularity of metaphyses in the distal of long bones, joint contractures, tubulation disorders of bones and kyphoscoliosis can be revealed. Our patient had physical examination, X-ray and laboratory findings of secondary hyperparathyroidism due to the rickets. In the present case, maternal P, ALP, 25(OH)D values were normal and mother was not hypocalcemic so we suggested a defect in placental calcium transport. Laboratory findings of secondary hyperparathyroidism, X-ray findings referring abnormal bone mineralization with typical dysmorphic features can be related with lysosomal storage diseases associated with skeletal dysplasia (dyzostosis multiplex group). GM1 gangliozidosis type1 or mucolipidosis type 2 was considered primarily in our patient. The patient was diagnosed with mucolipidosis type 2 due to high plasma enzyme activities and detected homozygous mutation on the GNPTAB gene; NM_024312.5 c.3091C> T (p.R1031*) (p.Arg1031Ter).

Patients usually die from respiratory system infections or congestive heart failure in early childhood [2,7]. In infantile type, the prognosis is worse. Though early characteristics and manifestations described I-cell disease can not be diagnosed in neonatal period until later in the infancy, our patient was diagnosed in the early neonatal period [8]. Cardiac assessment was normal. Respiratory distress resolved and he was discharged on the 45th day of his admission. On the day of life 52, he was deceased due to aspiration. Although its etiology is unclear, there are a number of hypotheses. The pathogenesis of severe hyperparathyroidism observed in the neonatal period in mucolipidosis type 2 is not fully known [9]. The authors suggest that the lysosomal enzymes targeting osteoclasts incorrectly, can lead to disruption of the biological feedback effect and induce PTH transduction, in a sense they consider dysfunction of calcium sensing receptors [5].

They also assume that targeting mannose-6-phosphate may be related to signal transduction on PTH effects on bone formation and remodeling. It has been demonstrated that Sox9 expression and collagen formation timing are effective in cartilage development and differentiation, and that production of extracellular matrix proteins is impaired in N-acetylglycosamine-1-phosphotransferase-inhibited zebrafish models, which causes many skeletal dysplasia [5]. Unger et al. suggested calcium transport disorder due to placental involvement as reason [7]. Although the placenta of our patient has not been examined, it is stated in the literature that placenta is affected in lysosomal diseases [10]. In histological examinations, widespread vacuolization due to the accumulation of macromolecules was observed in the cytoplasm of syncytiotrophoblasts where active transplacental transport was provided [10].

In normal physiology, calcium transfer from mother to baby increases in the last trimester. In our case, calcium,

phosphorus, vitamin D and parathormone levels may be normal in the first trimester. The impairment of calcium transport in the last trimester due to the progress of lysosomal disease may lead to intrauterine hypocalcemia and emerging bone destruction with increased parathormone and ALP thus keeping the calcium level within normal limits. Here we present a neonate having secondary hyperparathyroidism and lysosomal storage disease. Either prenatal or neonatal diagnosis is very important in this fatal disease. Further studies are needed to understand the pathophysiology of secnodary hyperparathyroidism and placental involvement.

References

1. Poorthuis BJ, Wevers RA, Kleijer WA, Groener JEM, et al. (1999) The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 105: 151-156.
2. Capobres T, Sabharwal G, Griffith B (2016) A case of I-cell disease (mucolipidosis II) presenting with short femurs on prenatal ultrasound and profound diaphyseal cloaking. BJR Case Rep 2: 20150420.
3. De Pace R, Coutinho MF, Koch-Nolte F, Haag F, Prata MJ, et al. (2014) Mucolipidosis II-related mutations inhibit the exit from the endoplasmic reticulum and proteolytic cleavage of GlcNAc-1-phosphotransferase precursor protein (GNPTAB). Hum Mutat 35: 368-376.
4. Otomo T, Higaki K, Nanba E, Ozono K, Sakai N (2011) Lysosomal storage causes cellular dysfunction in mucolipidosis II skin fibroblasts. J Biol Chem 286: 35283-35290.
5. Lin MH and Pitukcheewanont P (2012) Mucolipidosis type II (I-cell disease) masquerading as rickets: two case reports and review of literature. J Pediatr Endocrinol Metab 25: 191-195.
6. Kollmann K, Pestka JM, Kühn SC, Schöne E, Schweizer M, et al. (2013) Decreased bone formation and increased osteoclastogenesis cause bone loss in mucolipidosis II. EMBO Mol Med 5: 1871-1886.
7. Unger S, Paul DA, Nino MC, McKay CP, Miller S, et al. (2005) Mucolipidosis II presenting as severe neonatal hyperparathyroidism. Eur J Pediatr 164: 236-243.
8. Lemaitre L, Remy J, Farriaux JP, Dhondt JL, Walbaum R (1978) Radiological signs of mucolipidosis II or I-cell disease. A study of nine cases. Pediatr Radiol 7: 97-105.
9. David-Vizcarra G, Briody J, Ault J, Fietz M, Fletcher J, et al. (2010) The natural history and osteodystrophy of mucolipidosis types II and III. J Paediatr Child Health 46: 316-322.
10. Rapola J and Aula P (1977) Morphology of the placenta in fetal I-cell disease. Clin Genet 11: 107-113.