Rickets-like radiological and biochemical features of neonatal mucolipidosis II (I-cell disease): report of two cases

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SUMMARY: Türker G, Hatun Ş, Gülleroğlu K, Çizmeci F, Gökalp AS, Coşkun T. Rickets-like radiological and biochemical features of neonatal mucolipidosis II (I-cell disease): report of two cases. Turk J Pediatr 2005; 47: 376-378.

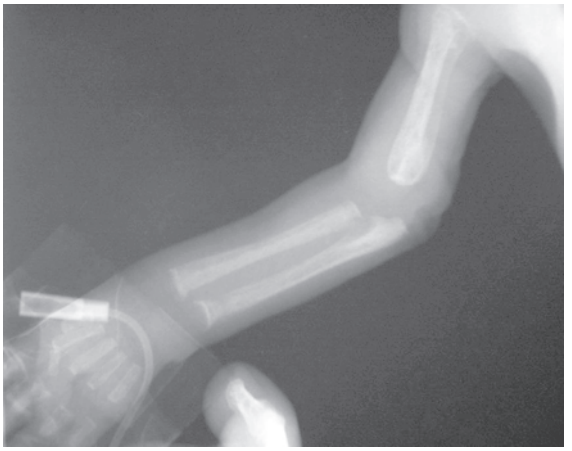
In this paper, two cases with mucolipidosis type II (I-cell disease) (proven in one presenting newborn and presumed in an elder deceased brother) are presented. These infants showed severe skeletal changes with diffuse periosteal new bone formation in long bones and ribs, marked osteopenia, and resorption of scapula, clavicula, and mandible. There was also irregular demineralization of metaphyses of long tubular bones, as seen in rickets. The activities of serum alkaline phosphatase and parathyroid hormone were markedly elevated. Phosphorus was decreased. Serum 1,25-dihydroxyvitamin D was slightly elevated, but 25-hydroxyvitamin D and calcium were normal. Dysostosis multiplex resembling rickets and very high alkaline phosphatase activity were due to defective osteoblastic activity, but the mechanism of elevated parathyroid hormone was not clear. We conclude that early skeletal manifestation of mucolipidosis type II is not clearly identified and that differentiation from congenital rickets or congenital hyperparathyroidism could be difficult. It is speculated that hyperparathyroidism in these patients could be related to the calcium-sensing receptor malfunction in the parathyroid gland.

Key words: I-cell disease, rickets-like sign, hyperparathyroidism, high activities of alkaline phosphatase.

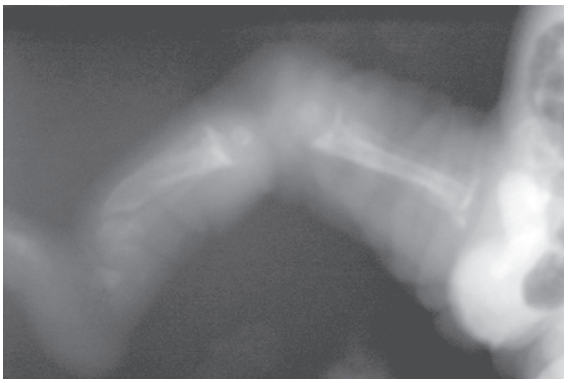
I-cell disease (mucolipidosis type II) is a rare, autosomal recessive lysosomal storage disorder[1]. The disease is characterized clinically by typically coarse facial features and by dysostosis multiplex rickets-like X-ray findings in early infancy[2-3]. The aim of this report was to speculate on the pathogenesis of rickets-like lesions, hypophosphatemia, high alkaline phosphatase activities and parathyroid hormone (PTH) in I-cell disease.

Case Report

A five-day-old male full-term newborn with a birth weight of 2400 g was admitted to our center with unconjugated hyperbilirubinemia. The mother reportedly had an uneventful pregnancy. The baby was the third child of nonconsanguineous parents. The first child of the family was a 10-year-old healthy girl. The second child died with pneumonia at two months of age in our center. This boy and his deceased brother had hyperplastic gums, coarse facies, puffy eyelids, long fingers, and bowed legs. X-ray showed severe skeletal changes including diffuse subperiostal demineralization of long bones and ribs, marked osteopenia, resorption of scapula, clavicula, and mandible, and irregular demineralization of metaphyses of long tubular bones (dysostosis multiplex rickets-like changes) (Fig. 1). The vertebrae of both children were radiologically normal. Serum biochemistry revealed markedly elevated activities of alkaline phosphatase (ALP) (1697 U/L, n: 164+68), hypophosphatemia [phosphorus (P) 3.87 mg/dl, n: 4.5-6.5 mg/dl], normal calcium (Ca) levels (9 mg/dl), hyperparathyroidism (PTH 325 pg/ml, n: 7-65 pg/ml), normal 25 hydroxyvitamin D (19.12 ng/ml, n: 20-60 ng/ml), elevated



(a)



(b)

Fig. 1a, 1b. X-ray showing severe skeletal changes including diffuse subperiostal demineralization of long bones, bowed legs and irregular demineralization of metaphyses of long tubular bones (dysostosis multiplex resembling the radiological features of rickets).

1,25 dihydroxyvitamin D (234 pmol/L, n: 43-148 pmol/L) and normal tubular reabsorption of phosphate (96.8%). Urinary Ca/creatinine (Cr) ratio was 0.13 (0.03 -0.9) and P/Cr ratio 0.04 (0.39-5.6).

Clinical and laboratory findings led to a diagnosis of I-cell disease, which was confirmed by the demonstration of high activities of B-hexosaminidase and B-mannosidase in the serum sample of the patient (Central Manchester and Manchester Children's University Hospitals, Willink Biochemical Genetics Unit, UK). The urine mucopolysaccharide analysis showed small amounts of dermatan and heparan sulfates. The serum biochemistry of the deceased brother had also revealed markedly elevated activities of ALP (1703 U/L), hypophosphatemia (P: 2.1 mg/dl), normal Ca levels (9.1 mg/dl), hyperparathyroidism (PTH: 728 pg/ml), and normal 25 hydroxyvitamin D (24 ng/ml). Serum biochemistry of the mother revealed normal levels of ALP (71 U/L), P (3.8 mg/dl, n: 3.5-5.5), Ca (9.7 mg/dl), PTH (70.8 pg/ml), and 25 hydroxyvitamin D (23 ng/ml).

Discussion

The clinical signs of hypertrophic gums, coarse facies, puffy eyelids, long fingers, and bowed legs were remarkable. I-cell disease is caused by a deficiency in the cells of the enzyme N-acetylglucosamine-1-phosphotransferase. This enzyme is responsible from the phosphorylation of lysosomal precursor enzymes. When phosphorylated, these enzymes bind to the mannose-6-phosphate receptor and are subsequently targeted into the lysosomes[4]. Neonatal skeletal radiographs are distinctive: a transient osteopathy in the form of dysostosis multiplex resembling rickets is present early in life, along with elevated serum activities of ALP and PTH, decreased phosphate despite normal Ca levels and proximal tubular function with normal P and Ca excretion. It is suggested that the early skeletal abnormalities of mucolipidosis type II are the result of a primary enzymatic defect of cartilage and bone cells or other factors controlling bone metabolism. Several explanations may be offered for the rickets-like lesions.

Dysostosis multiplex lesions first suggesting rickets were also present at birth in some other reported cases and in Turkish patients[5,6]. Pazzaglia et al.[3] reported that I-cell disease revealed inhibition of the growth plate calcification with defective vascular invasion and intracellular membrane-bound vacuoles in the chondrocytes, osteoblasts, osteocytes, and stromal fibroblasts. Osteoclasts and marrow cells were unaffected[3]. In I-cell disease, the corruption of osteoblast function due to a deficiency of the phosphorylation of lysosomal precursor enzymes causes ineffective osteoblastic activity; therefore, it is speculated that metaphyseal calcification is disharmonic. In our patients the early radiological rickets-like appearance of bones in the neonatal period and markedly high activities of ALP were possibly due to the affected chondrocytes, osteoblasts, osteocytes, and stromal fibroblasts and inhibition of the growth plate calcification as previously reported[3].

Hypophosphatemia and hypercalciuria with I-cell disease were also reported in a patient by Pazzaglia et al. in 1989[3] and Bocca et al. in 2003[8,9]. In other reports, information about the etiology of markedly high activities of PTH and normal Ca level has been lacking. The reason for hypophosphatemia was impaired renal phosphate reabsorption. This increased concentration inhibits phosphate reabsorption and maintains normal Ca due to apical expression of PTH receptor in proximal tubule cells (10-12). Bocca et al.[9] postulated that the lack of proteases in I-cell disease is responsible for impaired degradation of endocytosed low molecular weight proteins and interferes with cell-surface transporter recycling. These findings suggested that the reason for markedly high activities of ALP and normal 25 hydroxyvitamin D levels and normal or elevated 1,25 dihydroxyvitamin D may be ineffective osteoblastic activity and high bone turnover and hypophosphatemia.

Subperiostal demineralization is the sign of elevated PTH. The etiology for the high activities of PTH is not clear. A secondary etiology is not possible because of hypophosphatemia, normocalcemia, normal 25 hydroxyvitamin D levels and normal or elevated 1,25 dihydroxyvitamin D. Therefore, it could be speculated that the most probable defect causing elevated activities of PTH is in the secretion phase of PTH. At that point, the Ca-sensing receptor, which is a G protein-coupled receptor, has a key role in extracellular Ca homeostasis, regulating the secretion of PTH and the reabsorption of urinary Ca appropriate to the prevailing calcemic environment. In I-cell disease, secretion of hormones from several exocrine glands is corrupted due to intracellular membrane-bound vacuoles in the exocrine glands[13]. Further investigation is therefore required to confirm whether or not the cause of hyperparathyroidism could be related to a primary enzymatic and Ca-sensing receptor defect in the parathyroid gland.

REFERENCES

1. Beck M, Barone R, Hoffmann R, et al. Inter- and intrafamilial variability in mucolipidosis II (I-cell disease). Clin Genet 1995; 47: 191-199.
2. Pazzaglia UE, Beluffi G, Danesino C, Frediani PV, Pagani G, Zatti G. Neonatal mucolipidosis 2. The spontaneous evolution of early bone lesions and the effect of vitamin D treatment. Report of two cases. Pediatr Radiol 1989; 20: 80-84.
3. Pazzaglia UE, Beluffi G, Bianchi E, Castello A, Coci A, Marchi A. Study of the bone pathology in early mucolipidosis II (I-cell disease). Eur J Pediatr 1989; 148: 553-557.
4. Varki AP, Reitman ML, Konfeld S. Identification of a variant of mucolipidosis III (pseudo-Hurler polydystrophy): a catalytically active N-acetylglucosaminyl phosphotransferase that fails to phosphorylate lysosomal enzymes. Proc Natl Acad Sci USA 1981; 78: 7773-7777.
5. Güngör N, Coşkun T, Akçören Z, Çaglar M. I-cell disease: a case report and review of the literature. Turk J Pediatr 1994; 36: 145-152.
6. Hızel S, Coşkun T, Emre S, Hasıroğlu F, Tanyer G. A case of I-cell disease with rapid deterioration. J Inherit Metab Dis 1996; 19 (Suppl): 90.
7. Yashiro N, Abe T. Radiological features of neonatal mucolipidosis II (I-cell disease): a case report. Radiat Med 1985; 3 (2): 95-98.
8. Bocca G, Noordam C, Wevers RA, et al. I-Cell disease presenting with severe hypophosphatemia and cardiomyopathy. Neuropediatrics 2000; 31: 49-50.
9. Bocca G, Monnens LA. Defective proximal tubular function in a patient with I-cell disease. Pediatr Nephrol 2003; 18: 830-832.
10. Devuyst OO, Guggino WR Chloride channels in the kidney: lessons learned from knock-out animals. Am J Physiol Renal Physiol 2002; 283: F1176-1191.
11. Jentsch TJ, Stein V, Weinreich F, Zdebib AA. Molecular structure and physiological function of chloride channels. Physiol Rev 2002; 82: 503-568.
12. Marshansky V, Ausiello DA, Brown D. Physiological importance of endosomal acidification: potential role in proximal tubulopathies. Curr Opin Nephrol Hypertens 2002; 11: 527-537.
13. Ellender M, Martin JJ. Mucolipidosis type II with evidence of a novel storage site. Virchows Arch 1998; 433: 575-578.