Original Article

I-Cell Disease (Mucolipidosis II) Presenting as Neonatal Fractures: A Case for Continued Monitoring of Serum Parathyroid Hormone Levels

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Abstract. A severe form of I-cell disease (mucolipidosis II) can present in the newborn period as multiple fractures. The bone disease in these patients is believed to be due to hyperparathyroidism. We report a case where bone disease was present at birth but the parathyroid hormone levels were initially normal and did not increase until 37 d of age. Supplementation with vitamin D was needed to normalize the parathyroid hormone levels despite adequate intake of vitamin D, calcium and phosphorus. We suggest that in patients with I-cell disease, continued evaluation for hyperparathyroidism may be necessary despite initial normal parathyroid hormone levels.

Key words: I-cell disease, mucolipidosis II, hyperparathyroidism, vitamin D, rickets

Background

I-cell disease (mucolipidosis II, ML-II) is a rare autosomal recessive disorder due to a deficiency of phosphotransferase [UDP-N-acetylglucosamine: lysosomal enzyme N-acetylglucosaminyl-1-phosphotransferase] (1). Affected individuals have psychomotor retardation, skeletal abnormalities and organomegaly. Death in ML-II usually occurs by the fifth to eighth year secondary to bronchopneumonia, apnea or cardiac failure.

The clinical features of I-cell disease manifest in the first year of life but can almost always be found at birth. Radiographic findings in the neonate resemble changes of rickets and/or hyperparathyroidism and later develop into Hurler-type dysostosis multiplex (2–5). Congenital fractures are rare and likely the result of severe osteopenia and disorganized bone formation. Increased PTH levels at birth in children with I-cell disease and radiographic
changes in bone have led to an understanding that the primary cause of bone disease in these patients may be hyperparathyroidism (2, 3, 6).

We report the presentation of I-cell disease in the newborn period as multiple fractures and normal PTH levels at birth. This case is unusual because there were bony changes of hyperparathyroidism despite normal initial serum PTH levels, and this indicates that hyperparathyroidism may develop in patients with I-cell disease after the first month of life. We suggest continued monitoring of serum PTH levels in patients with I-cell disease even if the initial levels are normal and that vitamin D supplementation should be considered to treat the rise in serum PTH even if dietary intake of vitamin D is normal.

Case Report

A male infant was delivered at term and found to have multiple fractures (bilateral metaphyseal fractures of the humeri, upper shaft fracture of the right humerus, bilateral metaphyseal fractures of the tibiae, fibulae and femora and multiple rib fractures; Fig. 1). Biochemical abnormalities included a low level of serum phosphate at 2 d of age (0.82 mmol/L) and normal serum total calcium level of 2.07 mmol/L. The serum intact PTH level at 9 d of age was normal at 65 pmol/L. Alkaline phosphatase was 439 U/L at 2 d of age. The level of 25-OH vitamin D was normal (58.2 nmol/L) at 24 d of age. He had combined conjugated and unconjugated hyperbilirubinemia that responded to 30 mg ursodeoxycholic acid three times a day.

A diagnosis of I-cell disease was established based on the clinical, radiographic and biochemical results. The serum total hexosaminidase activity was significantly elevated (61400 nmol/h/mL), the serum Hex-B 36320 nmol/h/mL and Hex-B% normal at 59% (Dr. John Callahan, The Hospital for Sick Children, University of Toronto, Toronto, Canada). The family declined initiation of vitamin D, although the patient was on other medications at that time. The alkaline phosphatase level increased to 1092 U/L by 5 d of age, and the serum intact PTH level rose to 409 pmol/L by 37 d of age. The alkaline

Fig. 1 Plain radiography of the extremities at 2 d of age. There is generalized demineralization of the visualized bones with coarse trabeculation. Multiple fractures with healing can be seen involving the distal femora, tibiae, right proximal humerus, right distal radius and probably in the distal humerus and distal radius. Metaphyseal cupping and irregularity of the zone of provisional calcification are most prominent in the distal tibia, distal radius and ulna, suggesting rickets. Subperiosteal bone resorption is best seen in the metacarpals, distal ulna, fibulas, and proximal tibias, suggesting the presence of hyperparathyroidism.
phosphatase level increased to 2666 by two mo of age. By 4 mo of age, the family elected to start supplementation of vitamin D (ergocalciferol) at 200 IU orally twice a day. Within a month of starting vitamin D, there was normalization of the serum phosphate, PTH and alkaline phosphatase levels. Dietary analyses showed that infant’s intake of calories, protein, calcium, phosphate and vitamin D met the nutrient requirements prior to the rise in serum intact PTH (Fig. 2). The patient died shortly before 2 yr of age due to complications of congestive heart failure. An autopsy was declined.

Mutation analysis of the \( GNPTA \) gene showed a novel homozygous base-pair deletion at nucleotide 3232 (c.3232ΔT; Micheal Friez, Greenwood Genetic Center, Greenwood, South Carolina, U.S.A.).

**Fig. 2** Levels of serum total calcium (■), phosphate (□), alkaline phosphatase (○) and intact parathyroid hormone (PTH) (●) before and after use of Vitamin D.
Discussion

The findings of rickets-like changes on radiographs of newborn babies with I-cell disease and low calcium and elevated parathyroid hormone levels has raised the possibility that primary or maternal hyperparathyroidism may be the cause of the metabolic bone disease in these patients. Histologic features of both rickets (disorderly calcium deposition) and hyperparathyroidism (subperiosteal bone resorption and loss of bone mass) have been documented in babies with I-cell disease (3, 4). Patients with hyperparathyroidism with I-cell disease have experienced normalization of PTH levels after vitamin D supplementation (6), whereas the fractures have even been found to heal spontaneously when the PTH levels are normal (5).

In our case, the 25-OH vitamin D level was normal at birth, and the PTH levels were initially normal; however, radiographic findings of rickets and hyperparathyroidism were present. The unique circumstances of delayed vitamin D introduction in this case after the development of hyperparathyroidism and brisk return to normal after vitamin D supplementation supports the argument by Unger et al. (6) that impaired calcium delivery may be an underlying factor contributing to the rise in serum PTH levels. In our case, there may have been impaired calcium absorption despite normal levels of 25-OH vitamin D. We measured the intake of vitamin D, phosphorus, calcium, protein and energy and found them to all meet the recommended nutritional requirements prior to the rise of serum PTH. Therefore, we suspect that in our case, impaired calcium absorption or a higher vitamin D requirement may have contributed to the rise in serum PTH. Our results indicate that further understanding of the underlying pathophysiology in vivo of bone disease in I-cell disease patients at the biochemical level is needed since our patient had radiographic features of hyperparathyroidism that long preceded the elevations in the serum PTH levels.

The dual nature of bone pathology in I-cell disease has been proposed by Pazzaglia and colleagues (2–5). On the one hand, lysosomal storage osteopathy affects primarily bone formation with abnormal vacuolization in osteoblasts. Histologically, osteoclasts appear to be unaffected. However, new evidence suggests that mannose-6-phosphate containing acid hydrolases are preferentially secreted as pro-proteins by osteoclasts into the extracellular matrix (7). Therefore, it is possible that impaired lysosomal enzyme trafficking may be at the heart of bone disease in lysosomal storage osteopathies and a potential target of therapy with substrate reduction inhibitors and chaperones. If so, the reason why the bone disease has a phenotype of both rickets and hyperparathyroidism in I-cell disease patients is undetermined. The normal PTH and calcium levels at birth would not be consistent with bone disease caused by rickets that is severe enough to result in multiple fractures of this degree.

The mutation found in our patient, a homozygous base pair deletion at nucleotide 3232 (c.3232ΔT), has not been reported previously. A recent report by Plante et al. (8) identified a single founder mutation, c.3503_3504delTC, in a French Canadian population of the Saguenay-Lac-Saint-Jean region. In our case, both parents were of English heritage with descendants settling in New Brunswick, Canada, and later having mixed heritage with Canadian First Nations. The family surname and geographic location is not reported upon request to respect their privacy.

In summary, we report, to our knowledge, the first case of neonatal I-cell disease with delayed PTH elevation rapidly restored by vitamin D supplementation and suggest that patients with I-cell disease in the neonatal period should be closely monitored for hyperparathyroidism even when the initial serum PTH levels are normal.
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