Transient Secondary Neonatal Hyperparathyroidism: A Presenting Feature of Sialidosis Type 2

Abstract:
Sialidosis is a lysosomal storage disease caused by deficiency of alpha-N-acetyl neuraminidase-1 (NEU1). Sialidosis is classified into two main clinical variants: type I, the milder form of the disease, and type II, which can in turn be subdivided into three forms: congenital, infantile, and juvenile. We report a female patient with sialidosis type II presenting with the congenital form of the disease with thrombocytopenia, pulmonary interstitial thickening, and transient secondary neonatal hyperparathyroidism.
Introduction

Sialidosis (McKusick 256550) is an autosomal recessive lysosomal storage disorder that is caused by deficiency of alpha-N-acetyl neuraminidase (sialidase) activity. The disease is caused by accumulation of sialyloligosaccharides, sialylglycoproteins and glycolipids in the liver and various other tissues as well as vacuolation in the liver, bone marrow, brain, kidney, as well as several endocrine organs including the thyroid and adrenal gland (Bonten et al 1996). Sialidosis can be either type I or type II, with the main difference being the age of onset and dysmorphism. Type I sialidosis (nondysmorphic) generally presents between the ages eight and twenty-five with clinical manifestations including gait abnormalities, progressive impaired vision, bilateral macular cherry-red spots, mild mental retardation, seizures, and neuropathy and myoclonus syndrome (Achyuthan and Achyuthan 2001; Thomas 2001). In contrast, type II sialidosis (dysmorphic) is characterized by an infantile onset, with somatic deformations including coarse facies and diastosis multiplex, medial to major mental retardation and death before the first decade of life (Cole et al 1977). On the basis of age at the onset of symptoms, type II sialidosis is divided into three forms: congenital, infantile, and juvenile (Achyuthan and Achyuthan 2001; Thomas 2001).

Here is presented a case report of a girl with congenital form of type II sialidosis presenting biochemical and radiological findings of transient neonatal secondary hyperparathyroidism.

Case Report

The child was born at 37 weeks of gestation following an uneventful pregnancy. The mother was a 37-year-old G5 P5 L2 woman who had one healthy son. Two of her other pregnancies had terminated with in utero exitus at months five and six. One female baby presenting similar phenotypic features had died at another center at postnatal month six. The parents were first cousins of Turkish origin. A single antenatal ultrasound performed at 18 weeks
This fifth child of the couple was born by caesarean section because of fetal bradycardia at another hospital. The child was subsequently referred to our hospital at postnatal day one for further evaluation for recognizing atypical facial appearance and detecting leukocytosis and thrombocytopenia. She was noted to be small for gestational age with a birth weight of 2.1 kg (<10th percentile), head circumference of 31.5 cm (10th percentile) and a birth length of 43 cm (<10th percentile). Physical examination showed coarse face, puffy eyes, epicanthal fold, depressed nasal bridge, long philtrum, macroglossia, gingival hypertrophy, short trunk, umbilical hernia, and mild decrease in muscle strength and tonus. Skeletal survey at 1 week of age revealed subchondral resorption at the medial sides of proximal parts of both humeri and at distal part of left humerus, cupping at distal metaphysis of both ulnae, and bowing in both femurs, the metaphyses had irregular appearance, and the images were in favor of subperiostal resorption. The vertebrae of the patient were radiologically normal (Figures 1a-b). Considering congenital rickets with the findings on direct radiogram, biochemical tests were performed. On day 4 of life, levels of total serum calcium (9.2 mg/dL; reference range, 9-10.2 mg/dL) and phosphate (4.6 mg/dL; reference range, 4.5-6.5 mg/dL), and alkaline phosphatase (ALP) (332 IU/L; reference range, 95-350 IU/L) were normal. On further investigation, serum parathormone (PTH) was markedly elevated (271 pg/mL; reference range, 11-67 pg/mL), serum 25-hydroxyvitamin D [25(OH)D] was normal (25.7 ng/mL; reference range, 20-60 ng/mL) on day 9 of life. The following serum parameters were normal in a maternal blood sample: total Ca (9.6 mg/dL), phosphate (4.1 mg/dL), ALP (131 IU/L), PTH (25 pg/mL), 25(OH)D (22 ng/mL). During the first three-month-period, while serum calcium level remained normal, phosphate level decreased (2.3 mg/dL), ALP level evidently increased (1503 IU/L), PTH remained high (143 pg/mL), serum 25(OH)D level was normal (42.8 ng/mL). Urine studies performed concurrently showed that there was no urinary loss of phosphate, glucose, amino acids, or
protein. Vitamin D3 therapy (1000 U ergocalciferol/day) and 60 mg/day P04 were initiated orally. Clinical and laboratory findings primarily suggested the diagnosis of mucolipidosis (ML) type II. The diagnoses of ML II (I-cell disease) and ML III were excluded through intraleukocyte enzyme analyses. β-galactosidase activity was normal. Sialidosis was diagnosed by detecting sialidase activity as 0.788 U/mg (2% of normal) in fibroblast culture. Normal sialidase activity is 33.965 U/mg (100%). (Where U is specific activity represented by substrate hydrolysis of 1 UM/min). Follow-up at 10 months showed that the radiological features of hyperparathyroidism had resolved as had the biochemical features (ALP 278 IU/L, PTH 37.1 pg/mL, total calcium 9.6 mg/dL, phosphate 4.4 mg/dL). Vitamin D3 and oral phosphate treatments were stopped. The radiological changes, in particular in the ribs, evolved into typical dysostosis multiplex. She suffered recurrent aspiration pneumonias and died at 2 years of age.

Discussion

Both primary and secondary hyperparathyroidisms are rare disorders in the neonatal period. Neonatal primary hyperparathyroidism, typically caused by homozygous familial hypocalciuric hypercalcemia, is characterized by life-threatening hypercalcemia. In contrast, neonatal secondary hyperparathyroidism is caused by maternal/fetal hypocalcemia, and is characterized by low or normal serum calcium and skeletal changes that vary in severity from mild osteopenia to severe demineralization with fracture (Cole et al 1977).

Sialidosis is an autosomal recessive disorder, which is characterized by the progressive lysosomal storage of sialylated glycopeptides and oligosaccharides. Sialidosis type I is a milder, late-onset, normosomatic form of the disorder (Thomas 2001). The severe early-onset form, sialidosis type II, is associated with dysostosis multiplex, Hurler-like phenotype, mental retardation, and hepatosplenomegaly. Sialidosis type II patients are classified as those having the infantile-onset form who are relatively normal at birth, and those having the congenital-
onset form that manifests prenatally and is associated with ascites and hydrops fetalis (Achyuthan and Achyuthan 2001; Thomas 2001). Here is presented a patient with sialidosis type II who exhibited the congenital form of the disease with thrombocytopenia and pulmonary interstitial thickening, and presented with the radiological and biochemical signs of hyperparathyroidism. Review of the literature shows that some of the patients with ML II presented with features of “metabolic” bone disease rather than with signs of dysostosis multiplex in the neonatal period (Sathasivam et al 2006; Türker et al 2005; Lin and Pitukcheewanont 2012; David-Vizcarra et al 2010). However, this is the first report on a patient with sialidosis type II who presented with transient neonatal hyperparathyroidism. The feature of the patient was bone disease with increased serum PTH and ALP activity, decreased serum phosphorus concentration. However, in contrast to neonatal severe primary hyperparathyroidism, her total Ca level was normal. Those observations were consistent with severe secondary neonatal hyperparathyroidism. “Secondary” hyperparathyroidism resolved with supplemental 1000 IU/day vitamin D3 and 60 mg/day P04, orally, by age of 10 months. The patient developed typical clinical and radiological features of sialidosis type II later in the course, and died at 2 years of ages.

Etiology for newborns with ML II presenting with clinical and biochemical profiles resembling rickets remains unclear. Features of congenital hyperparathyroidism have been reported in ML II as early as 19 weeks of gestation (Babcock et al 1986). According to the review of the literature by Lin and colleagues, up to date, 20 cases with ML II were noted to have radiographic evidence of rickets, and 12 (9 male, 3 female) of 20 infants had documented biochemical profiles. All of those 12 patients had X-rays suggestive of rickets and presented with elevated serum ALP and PTH levels. Three patients had both normal calcium and phosphate levels. The others had low calcium levels, low phosphate levels, or both (Lin and Pitukcheewanont 2012).
Certain hypotheses have been suggested to explain the bone pathology in the cases with mucolipidosis. One is that the enzymatic targeting defect of ML II interferes with transplacental calcium transport, and diminishes placental calcium transfer with concordant increase in PTH secretion to maintain extracellular calcium at the expense of the skeleton (David-Vizcarra et al 2010; Lin and Pitukcheewanont 2012). This hypothesis is supported by the fact that the placenta of the fetus with ML II is abnormal, characterized by generalized vacuolization of the cytoplasm in the syncytiotrophoblastic layer where active transplacental transport is regulated (Babcock et al 1986). Similar histopathologic placental findings go for sialidosis, as well (Mahmood and Haleem 1989). Another possible unifying hypothesis is that there is defective targeting of lysosomal enzymes to the osteoclasts with abnormal biofeedback and induction of PTH receptor transduction. In a recent paper by David-Vizcarra and colleagues (2010), the pathophysiology of osteodystrophy in ML II was investigated. The phenomenon of “pseudohyperparathyroidism” characterized by tissue hypersensitivity to circulating PTH was described. They further hypothesized that mannose-6-phosphate targeting may be involved in signal transduction of PTH effects on bone formation and remodeling. The features of such osteodystrophy are not present in other lysosomal storage disorders except for galactosialidosis and sialidosis. Thus, it is reasonable to speculate that the osteodystrophy is related to the underlying biochemical disorder. Further investigation is, therefore, required to confirm whether the cause of hyperparathyroidism in mucolipidosis and sialidosis type II could be related to an impaired transplacental calcium transport or other factors controlling bone metabolism.
References


Figure 1 a-b X-ray showing severe skeletal changes including diffuse subperiostal demineralization of long bones, pulmonary interstitial thickening, bowed femurs, and irregular demineralization of metaphyses of long tubular bones.
Dear Editor,

Thank you very much for reviewers’ comments on our paper.

I prepared the revised paper taking into account the comments from the reviewer.

A list of changes is appended below.

**Responses to the reviewers’ comments**

1. Does the baby have “Primary” or “Secondary” hyperparathyroidism? I would think of secondary hyperparathyroidism, as there are normal Ca and low P levels. The title of this case report may mislead the reader. The discussion should point out more clearly.

The title was corrected as “Transient secondary neonatal hyperparathyroidism: A Presenting Feature of Sialidosis Type 2”. It was mentioned more clearly why the patient was considered secondary neonatal hyperparathyroidism in “Discussion”.

2. How would you explain the early (1 wk) rickets changes in this baby? As in secondary hyperparathyroidism with normal Ca and slightly low P (day 4 and 1st 3-month of age), such as it occurs in vitamin D deficiency, skeletal rickets changes are rarely seen.

Majority of previously published patients with mucolipidosis type II had similar laboratory findings to our patient’s, with markedly elevated serum ALP and iPTH levels, low P levels, and normal Ca levels, and normal proximal tubular functions with normal P and Ca excretion.

It is suggested that early skeletal abnormalities of mucolipidosis type II and sialidosis are the results of a primary enzymatic defect of cartilage and bone cells or other factors controlling bone metabolism. The most blamed mechanism, as mentioned in “Discussion” section of the manuscript, is that the enzymatic targeting defect of ML II and sialidosis type II interferes with transplacental calcium transport, and diminishes placental calcium transfer with.
concordant increase in PTH secretion to maintain extracellular calcium at the expense of the skeleton. Another possible unifying hypothesis is that there is defective targeting of lysosomal enzymes to the osteoclasts with abnormal biofeedback and induction of PTH receptor transduction. A further hypothesis is that mannose-6-phosphate targeting may be involved in signal transduction of PTH effects on bone formation and remodeling. However, there is a clear need for further systematic studies regarding the pathophysiology of the osteodystrophy in ML II and sialidosis type 2 beginning at birth or time of diagnosis.

3. Did you perform the “calcitropic” chemistries in the mother? 
The following serum parameters were normal in a maternal blood sample:  
Calcium (9.6 mg/dL), phosphate (4.6 mg/dL), ALP (131 IU/L), PTH (25 pg/mL), 25(OH)D (22 ng/mL). That information was added to “Case report” section.

4. The author stated “there was no urinary phosphate loss”, that is surprising. As hyperparathyroidism causes phosphate loss in the urine, what are the values of TRP and TmP/GFR at the time of hypophosphatemia, also what is the urine Ca level? 
Urinary tests were performed at three months of age. TRP in urine was 96.8%. The urinary Ca/creatinine (Cr) ratio was 0.18 (reference range, 0.03-0.9), P/Cr ratio was 1.45 (reference range, 0.39-5.6). However, also in other published cases with mucolipidosis type II exhibiting clinical and radiological findings of severe secondary hyperparathyroidism at birth, urinary analyses and biochemical analyses of blood samples of their mothers were interestingly found normal.

5. Has the patient been treated with P and vitamin D until 10 months-2 years of age (at the time of normal biochemistries)? If yes, it should not be concluded as “transient” in nature.
As biochemical parameters of the patient became normal at month 10, vitamin D3 and oral phosphate treatments were stopped. That information was added to “Case report” section.

6. What was 25-OHD level following the treatment? A thousand units a day of vitamin D3 is a high dose for babies.

25(OH)D level of the case at day 9: 25.7 ng/mL (reference range, 14-60 ng/mL)

Month 3: 42.8 ng/mL

Month 10: 60.1 ng/mL
7. In the discussion, hypothesis “tissue hypersensitivity to circulating PTH”, I would think that PTH should be low (not high as reported).

According to the hypothesis by David-Vizcarra and colleagues, a pseudohyperparathyroidism occurs characterized by tissue hypersensitivity to circulating PTH. The authors suggested that defective targeting of lysosomal enzymes to the osteoclasts could lead to disrupted biofeedback and induce PTH transduction. They further hypothesized that mannose-6-phosphate targeting may be involved in signal transduction of PTH effects on bone formation and remodeling.

8. The unit of PTH used in the paper should be consistent (page 2 line 38, page 3 line 14). And the unit of PTH in reference range (page 2 line 38) was incorrect (should be pg/mL, not pg/L).

These mistakes were corrected.

9. Figures are not clearly seen.

The figures were corrected.

10. English needs to be improved.

The language was corrected.