

ORIGINAL ARTICLE

Transient Pseudohypoparathyroidism as a Cause of Late-onset Hypocalcemia in Neonates and Infants

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Background/Purpose: Transient pseudohypoparathyroidism is a rare cause of late-onset hypocalcemia in neonates and infants. The purpose of this study was to investigate the clinical presentation and natural course of transient pseudohypoparathyroidism in neonates and infants.

Methods: From 1995 to 2006, 21 patients under 3 months of age were admitted to our department because of late-onset neonatal hypocalcemia. Among these, five were noted to have transient hypocalcemia, hyperphosphatemia and elevated serum parathyroid hormone levels. Their clinical data, biochemical findings and natural course were thoroughly analyzed.

Results: All five patients were boys with increased neuromuscular irritability as their initial clinical manifestation. Initial biochemical data showed calcium 1.5 ± 0.16 mmol/L, phosphorus 9.6 ± 1.5 mg/dL, intact parathyroid hormone 182 ± 93 pg/mL and tubular reabsorption of phosphorus $94.8 \pm 3.7\%$. Two of the patients had magnesium deficiency. After reduction of phosphorus intake and supplementation with calcium and/or magnesium as indicated, the biochemical derangements resolved in 28 ± 3 days.

Conclusion: Neuromuscular irritability is usually the initial clinical presentation of transient pseudohypoparathyroidism. Aside from delayed renal maturation, pseudohypoparathyroidism is also caused by magnesium deficiency. Such a disturbance usually resolves before 3 months of age. [*J Formos Med Assoc* 2008; 107(10):806–810]

Key Words: hyperphosphatemia, hypocalcemia, magnesium deficiency, pediatrics, pseudohypoparathyroidism

Neonatal hypocalcemia is traditionally divided into early-onset and late-onset forms based on the age of onset.¹ Late-onset neonatal hypocalcemia is defined as hypocalcemia occurring after the age of 3 days. It is usually symptomatic as an initial manifestation of hypoparathyroidism, vitamin D deficiency, or maternal hyperparathyroidism.^{1–3} The high phosphorus content of infant milk formula has also been claimed to cause late-onset neonatal hypocalcemia,^{4–6} but transient pseudohypoparathyroidism of neonates has rarely been reported as a cause.^{7–10} We therefore

conducted this study to review the medical records of patients with late-onset neonatal hypocalcemia in the last 12 years and to present the clinical data and the natural course of transient pseudohypoparathyroidism.

Methods

From 1995 to 2006, there were 41 patients younger than 3 months who were admitted to the Department of Pediatrics of National Taiwan

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University Hospital because of hypocalcemia, and had detailed medical records for analysis. Twenty-one were classified as late-onset neonatal hypocalcemia. The causes included hypomagnesemia with hypoparathyroidism in nine, idiopathic hypoparathyroidism in five, maternal hyperparathyroidism in one, and critical illness with hypocalcemia in one. Five patients had hypocalcemia, hyperphosphatemia, high tubular threshold maximum for phosphorus per glomerular filtration rate (TmP/GFR), and elevated plasma parathyroid hormone (PTH) levels, which were characteristic of pseudohypoparathyroidism. Neither consanguinity nor family history of neonatal hypocalcemia was found in these five patients. They also did not have any history of maternal diabetes mellitus, neonatal asphyxia, renal insufficiency, rhabdomyolysis, blood exchange transfusion, or use of diuretics and anticonvulsants.

All five patients were fed with infant formula with a calcium/phosphorus ratio greater than 1.5 before the development of hypocalcemia. There were no stigmata of Albright hereditary osteodystrophy, rachitic rosary, or congenital malformations detected in these patients during physical examination. All had spontaneous recovery from pseudohypoparathyroidism. The medical records of these patients were thoroughly reviewed and their clinical course was analyzed.

On admission, all five patients had blood chemistry evaluated, including serum creatinine, alkaline phosphatase (ALP), calcium, phosphorus, magnesium, and intact PTH (iPTH). Twenty-four hour urine collection was made to determine urinary calcium excretion, magnesium excretion,

tubular reabsorption of phosphorus (%TRP) and TmP/GFR, which was calculated by the equation previously reported.¹¹ Four patients were regularly followed-up between 2 months and 7 months (mean, 4.8 months), with serum electrolyte and plasma iPTH levels monitored during this period. The fifth patient was lost to follow-up after the age of 10 days till he was 5 months old.

Results

All five patients were boys and three were premature (Table 1). Their age at onset of pseudohypoparathyroidism ranged from 4 days to 54 days (mean, 25 days). Three had jitteriness, focal seizures, or generalized seizures as their initial clinical manifestation. No neurologic anomaly was detected in these cases. The other two were admitted because of respiratory distress after birth, and laboratory tests showed asymptomatic hypocalcemia after the age of 3 days.

None of these patients had evidence of renal insufficiency (Table 2). Their serum calcium level was 1.5 ± 0.16 mmol/L, serum phosphorus was 9.6 ± 1.5 mg/dL, and plasma iPTH level was 182 ± 93 pg/mL at diagnosis. Their serum ALP was 983 ± 672 U/L. Two patients had hypomagnesemia with hypocalcemia and elevated iPTH levels. Their serum magnesium levels were 0.5 mmol/L and 0.64 mmol/L, respectively. At that time, their urinary magnesium excretion was 0.03 mmol/day and 0.007 mmol/day, respectively. All five patients had elevated %TRP of $94.8 \pm 3.7\%$ and a high TmP/GFR of 11.5 ± 2.5 mg/dL.

Table 1. Auxological data

Patient	Sex	Gestational age (wk)	Birth weight (g)	Age at onset (d)	Neurologic symptoms and signs
1	Male	40	2500	52	Seizures
2	Male	36	2870	54	Seizures, jitteriness
3	Male	38	3600	7	Seizures
4	Male	35	1900	7	–
5	Male	36	3144	4	–
Mean \pm SD				25 \pm 26	

Table 2. Laboratory data at diagnosis

Patient	Age (d)	Creatinine (mg/dL)	ALP (U/L)	Ca (mmol/L)	P (mg/dL)	Mg (mmol/L)	iPTH (pg/mL)	Ccr (mL/min/1.73 m ²)	24-hr urine Ca (mg/kg/d)	%TRP	TmP/GFR (mg/dL)
1	52	0.4	1319	1.43	11.1	0.78	246	58.2	1.6	93.2	12.2
2	54	0.4	1992	1.3	7.6	0.8	309	32.7	0.4	90.0	7.3
3	7	0.46	734	1.66	8.5	0.5	85	46.7	0.4	98.4	11.8
4	7	0.8	515	1.45	10.9	0.64	149	17.5	0.6	93.7	12.2
5	4	0.6	356	1.66	10	0.86	120	25.4	0.3	98.7	14.1
Mean ± SD	25 ± 26		983 ± 672	1.5 ± 0.16	9.6 ± 1.5		182 ± 93			94.8 ± 3.7	11.5 ± 2.5

ALP = alkaline phosphatase; iPTH = intact parathyroid hormone; Ccr = creatinine clearance rate; %TRP = tubular reabsorption of phosphorus; TmP/GFR = tubular threshold maximum for phosphorus per glomerular filtration rate.

Four of the five patients were treated with calcium supplementation and infant formula with low phosphorus content. A magnesium supplement was given to the patients with hypomagnesemia. The biochemical data of one of the asymptomatic patients with hypomagnesemia (Patient 4) returned to normal limits even without calcium supplementation. Anticonvulsants were given to the three patients with seizures. All the medications were discontinued after treatment, which ranged from 3 to 26 days.

The biochemical data of the four patients who had regular follow-up were within normal limits between 25 and 32 days (mean, 28 ± 3 days) after disease onset. No hypocalcemia was noted in these patients in the following 4.8 ± 1.9 months of follow-up. The last patient (Patient 5) had normal serum electrolyte levels but elevated plasma iPTH of 120 pg/mL detected at the age of 10 days. He was lost to follow-up thereafter and showed up again at the age of 5 months. He was symptom-free during this period and his serum electrolyte levels were all within normal limits.

Discussion

Late-onset neonatal hypocalcemia is an uncommon electrolyte disorder in neonates.¹⁻³ It usually reflects an underlying pathologic condition, such as vitamin D deficiency, hypoparathyroidism, maternal hyperparathyroidism, and high dietary phosphorus load. Transient pseudohypoparathyroidism has also been reported as a cause of late-onset neonatal hypocalcemia. In this series, 15 out of 21 cases (71%) had hypoparathyroidism as the cause of late-onset neonatal hypocalcemia. Five patients had hypocalcemia, hyperphosphatemia, high %TRP, high TmP/GFR, and elevated iPTH levels, which were consistent with pseudohypoparathyroidism. The laboratory findings also distinguished these patients from those with hypoparathyroidism or excessive phosphorus ingestion.

All five patients in the present series were boys. Similarly, five of seven patients reported in

the medical literature were male.⁷⁻¹⁰ Because transient pseudohypoparathyroidism is seldom reported, the exact reason for the male predominance is still not well understood. Three of our patients were premature babies with gestational age between 35 and 36 weeks. It has been reported that preterm infants with gestational age more than 34 weeks had a significant renal response to PTH stimulation.¹² Therefore, it is less likely that renal resistance to PTH in these patients is related to their prematurity *per se*. Three of the five patients had seizures as their initial clinical manifestation, which is compatible with earlier observations of increased neuromuscular irritability as the major initial presentation.⁷⁻¹⁰ There was a wide range in terms of age of onset. All of our patients had their age of onset within 2 months, and three were detected within 1 week. The age of onset reported in the medical literature was within 20 days of age.⁷⁻¹⁰ In our series, those two patients who had a later onset of the disorder also had more severe biochemical findings and bone changes than others. This may imply that they had experienced a subclinical course for some time before their neuromuscular irritability was detected.

The laboratory data of the five patients were similar to those with transient pseudohypoparathyroidism previously reported.^{7,8} In our series, two patients had elevated serum ALP levels. One had a bone X-ray examined and prominent periosteal effects in both femurs were detected. They also had higher iPTH levels than the other three patients. Such findings were also noted by Minagawa et al.⁸ Impairment of the intercellular communication between osteoblasts and osteoclasts was proposed to explain such phenomena.^{7,8}

Minagawa et al demonstrated that three patients with transient pseudohypoparathyroidism had a brisk response of plasma and/or urine cyclic AMP to PTH infusion, but the phosphate response to PTH was sluggish compared with the controls.⁸ One of two cases reported by Fujisawa et al had similar findings.⁷ These data suggest that defects in intracellular signal transduction distal to cyclic AMP in the kidneys may be one of the underlying mechanisms. Because all of the cases later recovered

spontaneously, delay in the maturation of renal development is proposed as the etiology of transient pseudohypoparathyroidism.

Two patients in the present series had hypomagnesemia accompanied by pseudohypoparathyroidism. Low urine magnesium excretion in these two patients suggested the presence of magnesium deficiency. It was reported previously that magnesium deficiency can impair parathyroid function,¹³⁻¹⁵ and hypomagnesemia accompanied by hypoparathyroidism is a common cause in neonatal hypocalcemia.³ Such a cause was noted in nine out of 21 patients (43%) in this study.

End-organ unresponsiveness to PTH due to magnesium deficiency has also been reported.¹⁶⁻¹⁸ The fact that two patients in this study had elevated iPTH levels at a time of hypomagnesemic hypocalcemia, with one (Patient 4) having complete recovery after treatment with magnesium supplementation alone, implied that end-organ responsiveness to PTH in these two cases was impaired. It has been suggested that defective signal transduction of G-protein coupled receptors in the PTH target organ due to magnesium deficiency is responsible for this end-organ unresponsiveness.¹⁷

All of the patients recovered after a period of treatment with calcium and/or magnesium supplements and reduction of phosphorus intake. Although prescribing of a vitamin D analog has been reported,⁷⁻¹⁰ our patients recovered without treatment with a vitamin D analog. From our experience, calcium supplementation in infant formula with low phosphorus content is adequate for the treatment of such patients.

There was a wide variation of time of spontaneous recovery in patients with transient pseudohypoparathyroidism. Four patients, who had been regularly followed-up at our pediatric endocrine clinic, recovered spontaneously within 32 days after disease onset. The other one who was lost to follow-up after the age of 10 days was symptom-free and had normal serum electrolyte levels at the age of 5 months. The natural course of these patients was similar to that reported in the literature.^{7,8}

In summary, transient pseudohypoparathyroidism is a rare cause of late-onset hypocalcemia

in neonates and infants. In addition to delayed renal maturation, magnesium deficiency is another cause of this disorder. Such a disturbance usually resolves before 3 months of age.

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