CASE REPORT

Three cases of transient neonatal pseudohypoparathyroidism*

Stepan Kutilek (1), Martina Vracovska (1), Kamila Pecenkova (1), Hana Brozikova (1), Eva Rondzikova (1), Eliska Boskova (1), Richard Pikner (2), Zlatka Fejfarkova (2)

(1) Department of Pediatrics, Klatovy Hospital, Klatovy, Czech Republic

(2) Department of Clinical Biochemistry, Klatovy Hospital, Klatovy, Czech Republic

ABSTRACT

Neonatal hypocalcemia is defined as serum calcium (S-Ca) < 2.0 mmol/l in full-term newborns and <1.75 mmol/l in preterm newborns. Neonatal hypocalcemia is either early onset (<3 days of age) or late onset (>3 days of age). Newborns with hypocalcemia are often asymptomatic but may present with hypotonia, apnea, poor feeding, jitteriness, seizures, and cardiac failure. Signs of hypocalcemia rarely occur unless S-Ca drops below 1.75 mmol/l. Neonatal hypocalcemia can be a result of hypoparathyroidism (transient or primary), increased serum calcitonin, sepsis, asphyxia, hepatopathy, hypomagnesemia, high phosphate load, transient hypoparathyroidism, and, rarely, transient neonatal pseudohypoparathyroidism [transient resistance to biological actions of parathyroid hormone (PTH)]. We present the case of three boys (two with gestational age 39 weeks, one 36 weeks; none of them with either asphyxia or sepsis) with mild hypotonia, where S-Ca in the range of 1.67–1.9 mmol/l was detected within the first 3 days of life, together with hyperphosphatemia [serum phosphate (P) 2.5–2.6 mmol/l], normomagnesemia [serum magnesium (S-Mg) 0.77–0.88 mmol/l], normal alkaline phosphatase (ALP) activity (2.8–4.5 μkat/l), and high serum PTH (40–51 pg/ml; normal = 5–28). In spite of the gradual increase of S-Ca, the elevated serum PTH persisted beyond days 3, 4, and 6 in all three boys, together with normal or low-to-normal S-Ca, high or normal-to-high serum P, and no increases in serum ALP. The mothers' S-Ca, P, Mg, ALP, and PTH levels were within normal reference ranges. With regard to laboratory results, the diagnosis of transient neonatal pseudohypoparathyroidism (due to immaturity of PTH-receptors) is highly probable in these three neonates.

KEYWORDS

Calcium; Neonate; Hypocalcemia; Parathyroid hormone; Pseudohypoparathyroidism.

INTRODUCTION

In the course of fetal life, calcium (2.6–3.2 mmol/kg/day) and phosphate (2.1–2.5 mmol/

Correspondence to:
Stepan Kutilek,
Associate Professor of Paediatrics, Head of the Department of Pediatrics, Klatovy Hospital, Klatovy, Czech Republic.
Email: kutilek@nemkt.cz
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kg/day) in a constant molar ratio of 1.3:1.0 are actively transported across the placenta, as the human fetus requires approximately 30 g of calcium during gestation. The placental calcium transport is mostly influenced by the parathyroid hormone-related peptide (PTHrP) [1–4]. The transplacental supply of calcium (Ca) and phosphorus (P) is abruptly stopped at birth. This is followed by a drop in serum calcium (S-Ca) level. Consequently, as a result of a drop in S-Ca, PTH concentrations rise immediately after birth and remain high for the next 24–48 hours. PTH is effective in kidneys, where it increases production of calcitriol and stimulates renal tubular calcium reabsorption and phosphate excretion; and in bone, where it increases bone resorption. S-Ca is usually normalized within the first 3 days of life, same as the PTH level [1–4]. However, under certain conditions, hypocalcemia can persist for a longer time. Neonatal hypocalcemia is defined as S-Ca < 2.0 mmol/l in full-term newborns and <1.75 mmol/l in preterm newborns. Neonatal hypocalcemia is either early onset (<3 days of age) or late onset (>3 days of age). Newborns with hypocalcemia are often asymptomatic but may present with hypotonia, apnea, poor feeding, stridor, jitteriness, seizures, and cardiac failure. Signs of hypocalcemia rarely occur unless S-Ca drops below 1.75 mmol/l [5–8]. The underlying causes of neonatal hypocalcemia are very heterogeneous (Table 1).

Risk factors for early onset neonatal hypocalcemia include prematurity, sepsis, maternal diabetes, perinatal asphyxia, low calcium intake, maternal hyperparathyroidism, and resistance to PTH—pseudohypoparathyroidism. Late onset neonatal hypocalcemia is a result of phosphate overload, transient or primary hypoparathyroidism, hypomagnesemia, hepatopathy, or resistance to PTH. The early onset hypocalcemia usually requires treatment with calcium supplementation for at least 72 hours, while late onset hypocalcemia usually requires longer-term therapy [5–8].

We present the case of three boys with neonatal hypocalcemia, where transient pseudohypoparathyroidism was the most probable cause.

CASE REPORT

Patient No. 1 was a boy, spontaneously delivered by a healthy mother at the 39th gestational week. Birth weight was 3,790 g (75th percentile), birth length 54 cm (90th percentile); Apgar score of 8, 8, and 9. Physical examination was normal and there were no dysmorphic features. At the age of 3 days, neonatal jaundice (serum bilirubin 310 µmol/l) due to ABO incompatibility occurred together with mild muscular hypotonia. Blood tests further revealed hypocalcemia (total S-Ca 1.67 mmol/l), with serum phosphate level at the upper reference range and high S-PTH, with normal S-Mg and normal serum activity of alkaline phosphatase (S-ALP) (Table 2). The serum activity of aspartate aminotransferase (S-AST) and alanine aminotransferase (S-ALT) was within the normal reference range. Phototherapy was initiated and maintained for 37 hours; he was breastfed and, due to lack of maternal milk, he also received appropriate neonatal formula. He was also given intravenous (IV) infusion of 10% glucose and 10% calcium gluconate for 14 hours. On days 4 and 6, respectively, there was a slow improvement in S-Ca and the S-PTH remained increased (Table 2). He was discharged on day 9 and checked again on day 15, with normal values of S-Ca, P, Mg, PTH, ALP (Table 2), and a low serum 25-hydroxyvitamin D [S-25(OH)D] (33 nmol/l; reference range 75–150). The maternal levels of S-Ca, P, Mg, ALP, and PTH were normal.

Patient No. 2 was a boy with insignificant medical family history, delivered by Cesarean section on the 39th gestational week. Birth weight was 4,390 g (90th–95th percentile), birth length 52 cm (50th–75th percentile); Apgar score of 8, 9, and 10, respectively. Physical examination was normal and there were no dysmorphic features. At the age of 22 hours, muscular hypotonia and transient tachypnea were noticed. Laboratory assessment (blood count, C-reactive protein, procalcitonin, urinalysis, negative blood, and urine culture) ruled out neonatal sepsis. However, his S-Ca was 1.8 mmol/l, with high S-P and S-PTH, respectively (Table 3). Serum AST and ALT were within normal reference range. He received IV infusion of 10% glucose (250 ml)

Table 1 - Differential diagnosis of neonatal hypocalcemia.

Diagnosis	S-Ca	S-P	S-Mg	S-ALP	S-PTH
Asphyxia	↓	↔ ↓	↔	↔	↑
Transient hypoparathyroidism	↓	↑	↔	↔	↓
Primary hypoparathyroidism (DiGeorge syndrome)	↓	↑	↔	↔	↓
Hyperphosphatemia/phosphate overload	↓	↑	↔	↔	↑
Hypomagnesemia	↓	↑	↓↓	↔	↓
Vitamin D deficiency	↓	↓	↔ ↓	↑↑	↑↑
Maternal Ca/D-vitamin deficiency	↓	↔↓	↔	↔↑	↑
Pseudohypoparathyroidism Ia,b, II	↓↔	↑	↔	↔	↑
Transient pseudo-hypoparathyroidism	↓	↑ ↔	↔	↔	↑↑
Sepsis	↓	↔	↔↓	↔	↑
Hepatopathy	↓	↓	↔	↑	↑

Table 2 - Relevant biochemical parameters in Patient No. 1.

Parameter (units)	Age (days)				Reference values
	3	4	6	15	
S-Ca (mmol/l)	**1.67**	**1.92**	**1.97**	2.5	2.0–2.6
S-P (mmol/l)	2.5	2.5	**2.54**	2.4	1.5–2.5
S-Mg (mmol/l)	0.82	0.80	--	0.84	0.5–1.05
S-ALP (µkat/l)	3.3	--	--	2.32	2.4–9.5
S-PTH (pg/ml)	**40**	--	**34**	14	5–28
S-25(OH)D (nmol/l)	--	--	--	**33**	75–150

Table 3 - Relevant biochemical parameters in Patient No. 2.

Parameter	Age (days)				Reference values
	1	2	3	23	
S-Ca (mmol/l)	**1.8**	**1.94**	2.07	2.58	2.0–2.6
S-P (mmol/l)	**2.6**	2.5	2.5	2.36	1.5–2.5
S-Mg (mmol/l)	--	0.77		0.85	0.5–1.05
S-ALP (µkat/l)	--	--	2.83	5.56	2.4–9.5
S-PTH (pg/ml)	**40**	--	**39.6**	14.3	5–28

and 10% calcium gluconate (13 ml) at 14 ml/hour for 18 hours. Afterward, he was breastfed and received additional neonatal formula because of mother's insufficient lactation. There was a slow gradual improvement in S-Ca and a slow drop in S-P, however, S-PTH remained elevated and unchanged on day 3, with a normal value of S-ALP. He was discharged on day 6 and checked on day 23, with normal values of S-Ca, P, ALP, Mg, and PTH (Table 3). The maternal levels of S-Ca, P, Mg, ALP, and PTH were normal.

Patient No. 3 was a boy with insignificant medical family history delivered by Cesarean section on the 36th gestational week. His birth weight was 2,970 g (10th–25th percentile), birth length 50 cm (50th percentile), Apgar score of 7, 8, and 10, respectively. Tactile stimulation was necessary immediately after birth. Further physical examination was normal and there were no dysmorphic features. Due to hyperbilirubinemia (serum bilirubin 264 µmol/l at the age of 4 days), phototherapy was performed for a total of 24 hours. At the age of 4 hours, his S-Ca was at a normal-to-low value (Table 4). He received IV infusion of 10% glucose and 10% calcium gluconate together with IV amino acids because of his poor oral tolerance for the first 4 days; afterward, he was breastfed. There was an increase in S-Ca, with persistently elevated S-PTH and a very slow drop in S-P and no changes in S-ALP within the first 4 days of age (Table 4). On day 6, the S-Ca, P, ALP, and PTH levels were within normal reference ranges. He was discharged on day 14. The maternal levels of S-Ca, P, Mg, ALP, and PTH were normal.

DISCUSSION

Neonatal hypocalcemia due to end-organ-resistance to the biological actions of PTH [pseudohypoparathyroidism (PHP)] occurs rarely and can be either transient or persistent [4–8]. Persistent PHP is due to either PHP type I or II, a genetically determined defect of PTH receptors. Concerning transient PHP, Kruse et al. reported 26 preterm infants in 1987, where despite high S-PTH, the S-ALP, S-osteocalcin, urinary cyclic adenosine-monophosphate/creatinine ratio (U-cAMP/U-Cr), and urinary hydroxyproline/creatinine ratio were low during the first week of life. During the second and third weeks of life, the S-PTH decreased, while U-cAMP/U-Cr and bone turnover markers increased, reaching high-to-normal values in comparison with full-term infants [9]. The authors postulated that in premature infants, a transient end-organ-resistance was present during the first week of life due to the immaturity of renal and bone response to PTH [9]. Similarly, Schaumberger et al. [10] reported two infants with transient resistance to the biological action of PTH.

Minagawa et al. [7] presented three full-term infants aged 13, 27, and 30 days, respectively, with convulsions due to late onset hypocalcemia (1.8, 1.63, and 1.5 mmol/l, respectively), hyperphosphatemia, normomagnesemia, normal renal functions, normal S-25(OH)D, and high S-PTH, therefore suggesting transient resistance to PTH. The children showed an increase in cAMP secretion and S-ALP, with a sluggish response in phosphaturia after exogenous PTH infusion. The condition was considered as developmental and transient, possibly impairment of intracellular signal transduction distal to the cAMP formation,

Table 4 - Relevant biochemical parameters in Patient No. 3.

Parameter	Age (days)					Reference values
	0	1	3	4	6	
S-Ca (mmol/l)	**1.9**	2.11	2.22	2.38	2.4	2.0–2.6
S-P (mmol/l)	2.07	2.24	2.21	1.98	1.9	1.5–2.5
S-Mg (mmol/l)	0.88	--	--	--	--	0.5–1.05
S-ALP (µkat/l)	--	4.0	--	4.47	4.4	2.4–9.5
S-PTH (pg/ml)	--	**44**	**51.4**	**36.5**	19.7	5–28

a condition similar to the one observed in PHP type II. The S-Ca, S-P, and S-PTH normalized within 6 months of age [7]. Fujisawa et al. [11] reported two patients with transient neonatal PHP with similar findings.

Lee et al. described five boys (gestational age 35–40 weeks; three premature) aged 4–54 days with late onset hypocalcemia (S-Ca 1.3–1.66 mmol/l), hyperphosphatemia, high S-PTH, and high tubular reabsorption of phosphorus, consistent with transient neonatal PHP. All patients recovered after calcium supplementation [12].

Other reports on transient neonatal PHP always described a single neonate presenting with convulsions, where late-onset transient hypocalcemia and transiently increased S-PTH and S-P were the leading biochemical indices [13–18]. The condition, transient neonatal PHP, is therefore believed to be a result of immature PTH receptors in target tissues, occurring in both premature and full-term infants, presenting mostly as convulsions due to predominantly late-onset hypocalcemia [7–18].

Two of our patients (Patients No. 1 and 2) presented with hypocalcemia, normal-to-high S-P, normal S-Mg, normal S-ALP, and high S-PTH that persisted for at least 6 and 3 days, respectively, without corresponding increase in S-Ca and a drop in S-P. Patient No. 3 initially had low-to-normal S-Ca, normal S-P, with high S-PTH that persisted for at least 4 days, with a transient increase in S-P and gradual improvement of S-Ca; however, without any sharp increase in calcemia in spite of IV administered calcium gluconate and high S-PTH. Patient No. 1 was considered as having late-onset neonatal hypocalcemia, while Patients No. 2 and 3 were considered to have early-onset hypocalcemia. With regards to the differential diagnosis of neonatal hypocalcemia (Table 1) and based on our laboratory findings, we can certainly rule out hypocalcemia as a result of asphyxia, sepsis, hepatopathy, transient or primary hypoparathyroidism, pseudohypoparathyroidism type I or II, hypomagnesemia, phosphate overload, maternal diabetes, maternal hypercalcemia, and maternal hypocalcemia. Our patients were boys, which is in full accordance with other reports [7,11–18]. None of our patients presented with convulsions, unconsciousness, stridor, or cardiac failure.

We are aware of the limitations of our study as S-Ca^{2+}, albumin-adjusted-Ca, serum levels of 25-OH-vitamin D, urinary calcium and urinary phosphate concentrations were not assessed, with the sole exception of Patient No. 1, where S-25(OH)D was analyzed and found to be low.

Furthermore, S-ALP is considered a good marker to detect hyperparathyroidism in neonates, with a sensitivity of 78.6% and a specificity of 86.4% [19]. Therefore, in cases of severe vitamin D deficiency with resulting hypocalcemia and secondary hyperparathyroidism, high S-ALP and a drop in S-P should occur and that was not the case in our patients.

CONCLUSIONS

Neonatal hypocalcemia can be due to various causes, of which transient PHP is rather rare. Neonatal hypocalcemia is easily detectable, can be silent and self-limited, or manifest as a life-threatening condition.

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