Hypocalcemia in the newborn: analysis of clinical features and risk factors

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Abstract

Background: Neonatal hypocalcaemia (hypoCa) is frequently observed clinical and laboratory finding in neonates. A healthy newborn reaches the lowest serum calcium level at 24–48 hours of age. It can deteriorate to hypoCa levels in newborns with specific risk factors.

Methods: In the analysis, 50 newborns with hipoCa were included. Details of clinical signs and laboratory investigations were obtained from the available medical records and were statistically analysed.

Results: Early hipoCa was identified in 41 (82 %) and late in 9 (18 %) cases; 36 (72 %) were asymptomatic and 14 (28 %) symptomatic with the average serum calcium 1.8 (lowest 1.27) and ionized 0.92 mmol /l (lowest 0.63 mmol/l); 18 (36 %) infants had sepsis, 14 (28 %) were premature, 13 (26 %) mothers had gestational diabetes, three were after perinatal asphyxia, three after exchange transfusion, two after bleeding in twins and two had DiGeorge syndrome. Serum levels of 25-OH-vitamin D analysed in 13 newborns was lower than 52 nmol/l; 70 % of convulsions associated with HipoCa were due to vitamin D insuficiency.

Conclusion: Neonatal sepsis, maternal gestational diabetes, prematurity and vitamin D deficiency are the predominant risk factors. A low neonatal vitamin D reservoir can be associated with the development of PTH insufficiency, resulting in hipoCa, which can be presented with neonatal convulsions. The results suggest the need to establish guidelines for the prophylactic treatment of pregnant women with vitamin D.

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1. Background

Hypocalcaemia (hypoCa) in neonates may be a life-threatening condition or may just be found by laboratory tests and not manifested clinically. The occurrence of hypoCa depends on gestational age, associated diseases in both the mother and the neonate and perinatal risk factors (1). Due to variability of occurrence and clinical picture, the definition of hypoCa in the neonatal period is not strict; also the serum cut-off values for the introduction of treatment vary.

Serum calcium (Ca) is important for the maintenance of mineral homeostasis

in the body, cell processes, cell membrane stability, muscle fibre contractions, and transmission of signals along nerve fibres. For the maintenance of the balanced Ca level in the serum, parathormone (PTH), vitamin D and calcitonin, are most important, whereas the intake of Ca and phosphate (P), and serum magnesium (Mg) level also play a role (2)

During pregnancy, Ca is actively transported from the maternal to the foetal circulation via transplacental Ca pump regulated by parathyroid hormone-related peptide (PTHrP), produced by the placenta. Calcitonin and PTH do not cross the placental barrier. The greatest amount of Ca required for foetal bone mineralisation occurs in the third trimester, resulting in a higher Ca concentration in the foetus than in the mother; serum Ca levels in the umbilical blood range between 2.5 and 2.75 mmol/l, while the ionised Ca level is 1.5 mmol/l (3,4,5). After suddenly interrupted Ca transmission through the placenta at birth, the beginning of breathing triggers an increase in pH which contributes to the decrease of ionised Ca. Serum and ionised Ca decrease by 20–30 % within the first 12–24 hours after birth. The lowest Ca level is typically observed 24–48 hours after birth, but within a few days the serum and ionised Ca reach the levels as observed in adults (6,7).

Variable maturation of physiological mechanisms for maintaining serum concentrations of Ca and P, requiring complex interaction between the kidneys, the digestion system and the bones, leads to different definitions of neonatal hypoCa regarding gestational age and birth weight: in term newborns and in preterm newborns with birth weight higher than 1500 g hypoCa is defined at higher serum Ca level than in preterm newborns (7)

In neonates who develop moderate to severe hypoCa the first clinical signs are excessive jitteriness, tremor, food refusal and vomiting. With increasing hypoCa, apnoea, cyanosis, cerebral convulsions, stridor due to laryngospasm and wheezing above the lungs at bronchospasm may occur; electrocardiogram may reveal a prolonged QTc interval (6).

With regard to the time of occurrence of clinical signs there are two categories of hypoCa: early onset (within the first 24–48 hours) and late onset hypoCa (day 3–14 after birth); the former is usually caused by prematurity, associated neonatal diseases (neonatal sepsis, parathyroid gland agenesis), some maternal causes (gestational diabetes, antiepileptic drugs) or as a consequence of pregnancy, labour and specific conditions in the early neonatal period (perinatal asphyxia, intrauterine growth restriction, preeclampsia); and the latter is due to neonatal congenital disorders (primary hypomagnesaemia, DeGeorgee syndrome, hypercalciuric hypocalcaemia, metabolic syndrome), maternal factors (vitamin D deficiency, hyperparathyroidism) or it is iatrogenic (greater phosphate intake, fat infusion, bicarbonate infusion, citrate transfusion of blood preparations, phototherapy (3).

The aim of this study was to analyse clinical features and risk factors linked to hypoCa in newborns hospitalized at the Department of Neonatology of the Division of Paediatrics of the University Medical Centre Ljubljana. Additionally, our aim was to analyse the impact of vitamin D deficiency on the occurrence of hypoCa in the neonate.

2. Methods

Retrospectively we reviewed electronic and paper medical records of the newborns hospitalised at the Department of Neonatology between 2012 and 2016 whose diagnosis on di-

scharge was either Ca metabolism disorder (ICD-10 code 10 E83.5) or other neonatal hypoCa (ICD-10 code P71.1). In the patient search, the Informational System of the Division of Paediatrics was used. Neonatal period was defined as the first 28 days of the newborn's life, whereas in preterm babies (those born before the completed 37th gestational week) it was defined as the period up to completed 44 weeks postmenstrual age. The inclusion criteria for the diagnosis of hypoCa were serum Ca levels below 2 mmol/l and ionised Ca levels below 1.1 mmol/l in term infants and in preterm infants with birth weight more than 1500 g, and

Table 1: Characteristics of newborns with hypocalcaemia admitted to the Department of Neonatology, Division of Paediatrics, University Medical Centre Ljubljana.

	All n = 50 (%)	Vitamin D3 deficiency n = 13 (%)
Gender		
Male	33 (66)	9 (69)
Female	17 (34)	4 (31)
Birth weight regarding gestational age		
Small for gestational age	4 (8)	0
Appropriate for gest. age	44 (88)	10 (77)
Large for gestational age	2 (4)	3 (23)
Season of birth a)		
Spring	14 (28)	6 (46)
Summer	11 (22)	2 (15)
Autumn	6 (12)	1 (8)
Winter	19 (38)	4 (31)
Newborn of mother with gestational diabetes	13 (26)	6 (46)
Neonatal sepsis	23 (46)	3 (23)
Di George syndrome	2 (4)	1 (8)
Perinatal asphyxia	3 (6)	0
Vitamin D3 deficiency	13 (26)	13
Exchange transfusion	3 (6)	0
Twin-twin transfusion (donor)	2 (4)	0
Antiepileptic therapy in mother	1 (2)	0
Mother, drug/methadone user	2 (4)	1 (8)
Hypoparathyroidism	11 /15	9 /13
Early/Late hypocalcaemia b)	41 (82) : 9 (18)	7 (54) : 6 (46)

Legend: a) Spring (March–May), Summer (June–August), Autumn (September–November), Winter (December–February); b) Early hypoCa (within first 48 h after birth); late hypoCa (from day 3 of life on); PTH, parathormone..

serum Ca levels below 1.75 mmol/l in preterm infants with birth weight less than 1500 g (8). Early onset hypoCa was defined as that occurring within the first 48 hours of life, and late onset hypoCa as that occurring after 3 days of life.

We collected data on gestational age and birth weight, described clinical signs, age at hypoCa occurrence and the presence of risk factors (gestational diabetes in the mother, hypovitaminosis D, perinatal asphyxia, neonatal sepsis, transfusion). Additionally, we collected the data on the treatment of hypoCa and on laboratory values of serum Ca, ionised Ca, Mg, P, PTH and vitamin D (in the mother and the newborn).

Serum Mg levels 0.66–1.15 mmol/l, and serum P levels 1.8–3.3 mmol/l were taken as the reference values (8). Intact PTH levels 87 ± 11 ng/l on day 2 and 23 ± 4 ng/l on day 10 were considered normal (8). Vitamin D (25-OH vitamin D) was considered deficient at the level below 50 nmol/l, insufficient within the range 50–74.95 nmol/l, and normal within the range 75–125 nmol/l.

Statistical analysis was performed using the programme SPSS Statistics. The basic analysis consisted of calculation of mean values and standard deviations, as well as the minimal and the maximal value of the variable. The Pearson correlation coefficient was used to calculate the association between the variables.

The study was approved by the National Committee of the Medical Ethics of the Republic of Slovenia on 21 March 2012 (no. 38/02/12); it was one of the topics dealt with in the research programme J4–3606 (C) funded by the National Research Agency (ARRS)

3. Results

In the observed period, 50 newborns with hypoCa were managed at the Department of Neonatology, 17 (34 %) girls and 33 (66 %) boys. Their mean birth weight was 3067 ± 777 g, range 1015–5230 g; their mean gestational age was 38 ± 2.7 weeks, range 30–41 weeks; 14 (28 %) were preterm and 36 (72 %) were term. Early hypoCa was registered in 41 (82 %) newborns, and late in 9 (18 %) (Table 1).

In 7 (14 %) newborns convulsions occurred, and in 7 (14 %) tremor; the others did not show clinical signs of hypoCa. In symptomatic newborns the mean serum Ca level was 1.8 mmol/l, and that of ionised Ca 0.92 mmol/l.

Table 2: Laboratory characteristics of newborns with hypocalcaemia.

Variable	n	Median (min-max)	Reference values
Calcium, total (mmol/l)	50	1.77 (1.27–2.04)	2.0–2.75
Calcium, ionised (mmol/l)	24	0.96 (0.63–1.20)	1.1–1.36
Phosphate (mmol/l)	39	2.14 (0.82–4.22)	1.8–3.3
Magnesium (mmol/l)	40	0.7 (0.43–1.0)	0.66–1.15
iPTH (ng/l)	15	50 (3–434)	87 ± 11
25(OH)D newborn (nmol/l)	13	29.6 (10–52.3)	75–125
25(OH)D mother (nmol/l)	7	19 (17.5–65)	75–125

Legend: 25(OH)D, hydroxy vitamin D; iPTH, intact parathormone

The most frequent risk factors for the development of hypoCa were sepsis in 36 % of newborns, gestational diabetes in 23 % of mothers, and vitamin D deficiency in 13 newborns (Table 1); a combination of several risk factors was found present in several cases.

Serum 25-OH-vitamin D level, measured in 13 (26 %) newborns, ranged between < 10 nmol/l and 52 nmol/l, mean 29.6 nmol/l. In most newborns (92 %) in whom serum 25-OH-vitamin D level was measured, it was within the deficiency range (< 50 nmol/l), and in 1 in the insufficiency range (50–74.95 nmol/l). Of those, 7 (54 %) had early, and 6 (46 %) late hypoCa manifested with convulsions in 5 and with tremors in 3 newborns; 5 were symptom-free. Regarding the season of birth, most (77 %) were born in winter/spring months, and 23 % in summer/autumn months (Table 1). Serum 25-OH-vitamin D level, measured in 7 (14 %) mothers, was within the deficiency range in 6 (86 %) and within the insufficiency range in 1 mother.

The analysis of correlations between serum Ca levels and other biochemical parameters revealed statistically significant correlations between the levels of serum and ionised Ca and Mg, serum Ca and 25-OH-vitD in newborns, and between serum Ca and P. There were no statistically significant differences between the levels of Ca and PTH, and between vitamin D and other biochemical parameters in mothers (Table 3).

The analysis of therapeutic procedures showed that 41 (82 %) newborns received preparation of calcium gluconate i.v., 1 perorally, and 4 (8 %) received Ca intravenously and perorally. In 10 newborns the therapy included calcitriol (1.25-dihydroxycholecalciferol, ®Rocaltrol). In 20 newborns the therapy had to be continued after discharge from hospital in home care: 7 were receiving calcitriol and 3 calcium gluconate perorally. All newborns were receiving vitamin D in a prophylactic dose, and 13 in a therapeutic dose.

4. Discussion

Our results show that the incidence of hypoCa among the newborns hospitalised at the Department in the observed period was 1.44 %, although we are aware that some symptom-free newborns with likely border Ca levels remained undiagnosed. While the incidence of hypoCa in the neonatal period has not been clearly defined in the literature, it is rather frequent in paediatric intensi-

Table 3: Correlation between serum ionised and total calcium and other laboratory parameters.

Calcium	Mg	iPTH	25(OH)D	P
Ionised calcium	0.665**	0.111	0.147	-0.224
P-value	0.002	0.732	0.685	0.17
Total calcium	0.500**	0.353	0.603*	-0.58*
P-value	0.001	0.197	0.029	0.015

Legend: iPTH – intact parathormone; P – phosphate; Mg – magnesium; 25OHD – 25-hidroxy vitamin D; ** Correlation is significant at 0.01 (t-test for 2 samples); * Correlation is significant at 0.05 (t-test for 2 samples).

ve care units; the incidence reported in the literature ranges between 18 and 35 % (9). Numerous studies on heterogeneous groups of adult and paediatric populations in intensive care units have examined the association between hypoCa and fatal outcome (10,11). Zhang and co-workers found that mild hypoCa is protective, whereas moderate and severe hypoCa was related to increased risk of fatal outcome in children (12). On the other hand, Dias and coworkers have found that hypoCa is not a predictor of death, but is rather independently related to a severe failure of organ function (13).

A useful approach to classification of neonatal hypoCa regarding aetiology is the time of occurrence; in our study, early hypoCa was diagnosed in two thirds of newborns who had various risk factors and pathophysiologic mechanisms. Prematurity was one of the most frequent factor for early hypoCa as it occurred within the first 48 hours after birth in all of them. The causes for a substantial decrease of serum Ca in preterm infants have not been clarified yet. Transient relative hypoparathyroidism may lead to hypoCa in preterm infants and in small for gestational age newborns in whom parathyroid glands are less mature. To this condition low serum protein concentrations and pH, decreased Ca intake due to small enteral intake, inappropriate renal tubular cell response to PTH, and increased calcitonin levels are often associated; in addition, in preterm infants great secretion of sodium with urine increases calcium loss (6,14). We presume that most preterm infants were symptom-free since the decrease in serum Ca is usually greater than the decrease in ionised Ca, which is the consequence of hypoalbuminaemia, and in some cases of metabolic acidosis, which increases ionised Ca.

One fourth of newborns in our study had mothers with gestational diabetes, and in most of them hypoCa occurred within the first 48 hours after birth. HypoCa, which has been reported in 10–20 % of newborns of mothers with gestational diabetes having the lowest Ca levels 24–72 hours after birth, is frequently associated with hyperP and lower PTH concentrations (15). Due to Mg loss via the kidneys, mothers with gestational diabetes develop hypoMg, and consequently the foetus suffers from Mg deficiency, which leads to functional hypoparathyroidism in the foetus and later in the newborn (6).

In perinatal asphyxia, present in some newborns in our study, several factors contribute to early hypoCa: serum calcitonin increases and inhibits Ca release from bones; also, P serum level increases on the account of decreased glomerular filtration, which may lead to a relative unresponsiveness to PTH.

The most common cause for hypoCa in our study was neonatal sepsis present in 36 % of the newborns. Sepsis is a well-known risk factor which increases the risk for hypoCa via different mechanisms. According to some studies Ca passes from the extracellular space into the cell, whereas in the septic state the hormonal response to the occurrence of hypoCa is inappropriate (8). On the other hand there are authors who consider acquired disorders of parathyroid glands, vitamin D deficiency in food, and renal hydroxylase deficiency a possible cause for the occurrence of hypoCa in patients with sepsis. Some researchers claim that in patients with sepsis hypoCa is related to the inflammatory response and/or to the effects of inflammatory mediators (higher increased cytokine and catecholamine production) on PTH secretion and function, and target organ resistance to treatment (16.17). It is not known

whether hypoCa triggered by sepsis may have protective or damaging effects on the patient; also, there is no evidence for routine Ca replacement in septic patients (18).

Biochemical characteristics of hypoparathyroidism are hypoCa and hyperP along with the normal renal function and an undetectable serum PTH concentration. The causes for hypoparathyroidism are various, disorders in the development of parathyroid glands being one of them. HypoCa accompanied by hypoparathyroidism is one of the first clinical features of the Di Georgee syndrome, in which aplasia or hypoplasia of the parathyroid glands is often present (15).

In all the newborns and their mothers who had vitamin D concentration measured, the deficiency was found present. Hypovitaminosis D may be a risk factor for early or late hypoCa which was confirmed in our study. Additionally, we found that most newborns with convulsions accompanying hypoCa also had vitamin D deficiency. In pregnancy vitamin D crosses the placenta making a reservoir of vitamin D in the newborn – a correlation has been found between vitamin D concentrations in the mother and the newborn (19). In our study, 25-OH-vitamin D was measured in only half of the mothers and their newborns, the sample being thus too small to confirm potential relationships, yet it was evident that the concentrations were low. The findings of a study on vitamin D status in healthy pregnant women in Slovenia revealed that vitamin D was found deficient in 14 %, and insufficient in 41 %, whereas optimal concentrations were found in less than one half of healthy pregnant women (20). Furthermore, this study also showed inconsistency between the intake of vitamin D in normal eating habits and recommended intake levels (20). Contrary to most other developed countries, Slovenia has not yet approved clear recommendations on adding vitamin D to the diet in pregnant women.

Low 25-(OH)-vitamin D concentrations are usually associated with increased PTH concentrations, whereas in our study PTH was increased in one third of the subjects only. Low PTH has been associated with low Mg concentrations in neonatal hypoCa – in our study Mg levels were within the normal limits in most newborns with hypovitaminosis D. A possible explanation is that low vitamin D concentrations in the mother led to secondary hyperparathyroidism in the mother, which caused transient hypoparathyroidism and hypoCa in the newborn.

Furthermore, antiepileptic drugs may contribute to vitamin D deficiency. It is known that they increase vitamin D degradation in the liver and the tendency to vitamin D deficiency, which was the case of one newborn with early asymptomatic hypoCa in this study: the mother was treated with valproic acid treatment.

Seasonal variation of the incidence of neonatal hypoCa, (i.e. lower incidence in summer months) would support the aetiologic role of vitamin D deficiency (1), however our results confirm this only partly: among the newborns with vitamin D concentration measured, most were born in winter or spring, which is in agreement with the fact that the exposure to UV radiation in autumn and winter is lower, producing less vitamin D in the skin, leaving a smaller amount for the transfer to the foetus in the last months before birth (21).

Although it is not surprising, it should be mentioned that in our patients Ca and Mg correlated. Mg is necessary for both PTH secretion and for peripheral responsiveness to PTH (22). Decreased

PTH secretion due to hypomagnesaemia can partly be regulated by increased PTH secretion as a response to hypoCa, which is the consequence of the changes in the responsiveness to PTH. Co-existence of various biochemical imbalances in newborns indicates a synergistic role of hypoparathyroidism, vitamin D deficiency and hypomagnesaemia for the occurrence of hypoCa.

Beside the fact that in most cases asymptomatic neonatal hypoCa eventually spontaneously wears out, it may exert harmful effects on the cardiovascular system and the central nervous system, therefore treatment is necessary. In every newborn with risk factors it is necessary to verify the levels of serum and ionised Ca, since the treatment of hypoCa is accessible and efficient. As most causes are transient, the duration of treatment varies according to the cause; in early hypoCa Ca replacement on day 2 or 3 usually suffices, whereas a long-term treatment is necessary in cases of malabsorption, vitamin D deficiency, or hypoparathyroidism. The newborns with hypoCa in this study were treated according to these principles. Regarding the results of the studies on vitamin D deficiency in the general population, it would be advisable to consider the introduction of prophylactic treatment, which has been the case in newborns, also in pregnancy.

This study has several limitations. The sample size is small, and some data are missing for the retrospective nature of the study. These facts made the analysis of all possible factors causing the development of hypoCa difficult, especially the analysis of correlations between low vitamin D concentrations in newborns and their mothers. As some newborns with hypoCa are being treated in other intensive care units in the country, we could not estimate the incidence of neonatal hypoCa for entire Slovenia. In spite of this, the study is important since it provides an overview of the risk factors for the development of hypoCa in newborns in the Slovenia and the need for the introduction of prophylactic treatment with vitamin D already in pregnancy.

5. Conclusion

Neonatal hypoCa is a rare clinical condition of newborns treated at the Department of Neonatology. Sepsis, gestational diabetes in the mother, prematurity, and vitamin D deficiency were predominant risk factors in this study. Our findings support the hypothesis that low vitamin D concentrations in the newborn may be related to the development of hypoPTH and further of hypoCa. Our results also indicate the importance of accepting the guidelines for prophylactic treatment of pregnant women with vitamin D.

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