



Neonatal hypocalcemic Seizures: About a 41-Day-Old Infant

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OB and AR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OB and AR managed the analyses of the study. Author OB managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Neonatal crises have several etiologies. Hypovitaminosis D and hypocalcemia are the most common cause of childhood seizures, but their frequency has been reduced due to vitamin D supplementation and infant formula. Most hypocalcemic crises have an underlying endocrinological origin rather than a deficit in intake. We describe the case of a 41-day-old infant admitted for neonatal seizures for hypocalcemia. Although symptoms and concentrations of calcium and parathyroid hormone (PTH) levels favored isolated congenital hyperparathyroidism after eliminating other differential diagnoses. The course of the disease was favorable with intravenous (IV) calcium gluconate 10%, then orally alfacalcidol and vitd2. The case is presented with a brief review of the pathophysiology, differential diagnosis and treatment of neonatal hypocalcemia.

Keywords: *Seizures; neonatal hypocalcaemia; parathyroid hormone.*

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1. INTRODUCTION

Neonatal hypocalcemia is a serious disease and can be fatal in some cases. Its prevalence varying according to gestational age, perinatal factors, maternal and infant comorbidities [1]. It is defined as a serum calcium concentration of less than 80 mg / L (2 mmol / L) or an ionized calcium level below 48 mg / L (1.2 mmol / L) in term infants and a total calcium level below 70 mg / L (1.75 mmol / L) or ionized calcium 40 mg / L (1 mmol / L) in premature babies [2]. The calcium regulation begins in utero. The active transfer of calcium from the maternal circulation to the fetus occurs mainly during the third trimester of pregnancy via a transplacental calcium pump under the effect of a peptide linked to the parathyroid hormone (PTH). This process results in a higher plasma calcium concentration in the fetus than in the mother, so there will be term fetal hypercalcemia reaching 100 to 110 mg / L (2.5-2.75 mmol / L) in the blood of the cordon [3]. Transplacental transfer suddenly stops after birth. Serum calcium levels begin to drop during the first hours of life, reaching a minimum on the second or third day of life, then the calcium level increases to reach normal values on the tenth day of life [3]. This regulation after birth depends on dietary calcium intake, skeletal calcium stores, PTH secretion, vitamin D levels, renal and digestive calcium reabsorption [4]. The integrity of the cell membrane and cell functioning require a constant extracellular calcium concentration which plays a role in neuromuscular excitability, as a second messenger, cofactor in blood coagulation [5]. Neonatal hypocalcemia in tetany, nervousness, convulsions generalized or focal, muscle twitching, wheezing (bronchospasm) [6,7], laryngeal stridor (laryngospasm) [8], vomiting (pylorospasm), attribution of qtc on electrocardiogram [9], and poor muscle contractility [10]. The severity of neonatal hypocalcemia may vary mild to life threatening [11]. We describe the case of a 41-day-old infant admitted for neonatal seizures for hypocalcemia. Although symptoms and concentrations of calcium and parathyroid hormone (PTH) levels favored isolated congenital hypoparathyroidism after eliminating other differential diagnoses. The course of the disease was favorable with intravenous (IV) calcium gluconate 10% then orally, alfacalcidol and vitd2. The case is presented with a brief review of the pathophysiology, differential diagnosis and treatment of neonatal hypocalcemia.

2. CASE REPORT

A 41-day-old girl, the only child of non-consanguineous parents. It was delivered by caesarean section at 39 weeks gestation after an uncomplicated pregnancy (with no notion of gestational diabetes, no medication, no metabolic or endocrine disorders). Birth weight was 2,800 kg with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. There were no postnatal complications. The infant is fed infant formula. She presented to pediatric emergencies on the 8th day of life after 6 episodes of myoclonus of the lower limbs and tonic-clonic seizures of the 4 limbs for approximately 5 min without the postictal state. She was hospitalized in a neonatal intensive care unit for management, where an initial assessment was carried out and found hypocalcemia. She was therefore put on alfacalcidol 1 ug / d with a good clinical course marked by the disappearance of seizures. The cessation of treatment triggered the resumption of his convulsive symptoms, thus justifying his hospitalization. The patient was admitted to our department for further investigation and treatment. The Physical examination revealed an active afebrile baby, with the good axial and peripheral tone, with a normal facial appearance. The Paraclinical examinations included a complete blood cell count, a urinalysis and a cerebrospinal fluid analysis which were within the reference range. Blood chemistry revealed a calcium level of 58 mg / L (80–105 mg / L) and a phosphorus level of 105 mg / L (45–67). Endocrine function tests showed an intact serum PTH (ipth) level of 6.5 pg / ml (16–87 pg / ml). The maternal check-up was without anomalies. Renal ultrasound, chest x-ray, echocardiography, brain ultrasound and electroencephalography revealed no abnormalities. The fluorescent in situ hybridization test for a microdeletion on chromosome 22q11 was negative, excluding digeorge syndrome. The patient was put on intravenous (IV) calcium gluconate 10% then orally (elemental calcium 50 mg/kg per day), alfacalcidol 2 ug then 1ug / d and vitd2 800-1200UI / d. Evolution has been marked by the disappearance of seizures and myoclonus with normalization of serum calcium and phosphorus levels. The most likely diagnosis is Isolated hypoparathyroidism.

3. DISCUSSION

The neonatal convulsions secondary to hypocalcemia was reported for 100 years by

Kehrer in 1913 [12]. According to several studies that have been done in this sense, it constitutes the most frequent aetiology of neonatal convulsions [13]. Due to improved infant formula, the prevalence of hypocalcaemia has dropped to as little as 3% of neonatal seizures [14,15].

Neonatal hypocalcemia is classically divided into 2 categories: Early which manifests itself in the first 24 to 72 hours of life, and late between 4 and 28 days (Table 1).

Early hypocalcemia may be secondary to maternal factors (preeclampsia, gestational diabetes, use of anti-convulsants, maternal hyperparathyroidism and vitamin D deficiency), or by fetal factors (growth retardation intrauterine, prematurity and perinatal asphyxia), or caused by neonatal pathologies (neonatal respiratory distress syndrome, neonatal sepsis, neonatal icterus, hypomagnesemia and renal failure) [16].

The neonatal hypocalcemia can reveal asymptomatic primary hyperparathyroidism in her mother, hence the importance of careful evaluation not only of the newborn but also of her mother to discover and treat possible hyperparathyroidism in the mother. Maternal hyperparathyroidism causes elevated serum calcium levels in the fetus that inhibit the parathyroid glands from synthesizing fetal PTH. At birth, the newborn is brutally deprived of this rich source of calcium. It is unable to mobilize calcium from the bone due to low PTH and high concentrations of calcitonin. Acute neonatal hypocalcemia leads to tetany and convulsions, usually between 5 and 14 days. Routine blood tests show hypocalcemia with an abnormally low ipth level. Hypomagnesemia is also common.

Late hypocalcemia can be classified into 2 categories according to the level of PTH:

- The low PTH level may be secondary to a defect in the synthesis or release of PTH (dyshormonogenesis) or an error in the embryogenesis of the parathyroid gland (hypoplasia/aplasia). Hypoparathyroidism may be in the context of a syndrome (digeorge syndrome, Barakat syndrome, Sanjad-Sakati syndrome, Kearns-Sayre syndrome), or isolated (GCM2, PTH, SOX3), or secondary to activating mutation of the calcium-sensitive receptor [17,18].
- The late hypocalcemia with high PTH levels will be observed in pseudohypoparathyroidism, also during secondary

hyperparathyroidism by the consumption of milk rich in phosphorus or a deficiency of vitamin D. Iatrogenic causes (diuretics, transfusion of blood products citrate, phosphate therapy, phototherapy and glucocorticoids). Magnesium is necessary for both the secretion of PTH and the peripheral reactivity to PTH, for this Hypomagnesemia is a risk factor has not to forget hypocalcemia, which can be primary or secondary to other diseases [19].

The physical examination must be systematic in search of cleft palate, facial anomalies, and asymmetrical weeping face in terms of syndromic hypocalcemia. Blood tests: Ionized calcium, phosphate, albumin (calcemia corrects), total serum calcium level, magnesium, alkaline phosphatase, and creatinine levels will be requested. The levels of PTH, 25 OH Vit D, urinary calcium and creatinine should be measured. For patients with hypercalciuria despite hypocalcemia, familial hypercalciuric hypocalcemia (activating mutation of calcium-sensitive receptors) will be suspected. The level of PTH that is low or abnormally normal despite hypocalcemia may be seen in hypomagnesemia or during primary hypoparathyroidism. In hypoparathyroidism, the serum calcium level decreases, while the serum phosphate level increases. If the PTH level is raised secondarily to hypocalcemia, the parathyroid glands will be intact, and serum phosphate levels should be evaluated for diagnosis. If the serum phosphate level is low, a nutritional deficiency of vitamin D or malabsorption of vitamin D or genetic disorder of vitamin D metabolism disorders of vitamin D metabolism should be brought up. If elevated serum phosphate levels with increased PTH levels in response to hypocalcemia, renal failure, excessive exogenous phosphate intake, or pseudohypoparathyroidism (PTH resistance) should be considered. Serum creatinine levels and blood urine nitrogen levels should be measured to assess kidney failure.

Hypocalcemia may be secondary to hypomagnesemia and may be due to tubulopathy, osmotic diuresis, diuretics, or gastrointestinal loss (chronic diarrhoea, malabsorption), intrauterine growth retardation, intestinal magnesium transport disorders, maternal diabetes, maternal magnesium deficiency, nephrocalcinosis with hypercalciuria. Serum magnesium should be measured in patients with hypocalcemia who are resistant to treatment [20,21]. There is a state of functional

Table 1. Causes of early and late-onset hypocalcemia in the newborn period and infancy

Early-onset hypocalcemia	Late-onset hypocalcemia
<ul style="list-style-type: none"> • Prematurity • Intrauterine growth retardation (low birth weight) • Preeclampsia • Asphyxia (pseudohypoparathyroidism) • Sepsis • Infants of diabetic mothers • Severe maternal deficiency of vitamin D • Maternal hyperparathyroidism • Mother using anticonvulsants (phenytoin sodium, phenobarbiturate) • Maternal intake of high-dose antacids • Use of aminoglycosides and anticonvulsants in the newborn • Iatrogenic (alkalosis, use of blood products, lipid infusions and diuretics, phototherapy) 	<ul style="list-style-type: none"> • Increased phosphate load (feeding with cow milk, feeding with high-fibre formula, renal failure) • Hypomagnesemia • Vitamin D deficiency • PTH resistance • Hypoparathyroidism <p>Primary hypoparathyroidism</p> <ol style="list-style-type: none"> 1. Isolated hypoparathyroidism (GCM2, PTH, SOX3) 2. Casr activating mutations (hypercalciuric hypocalcemia) 3. Syndromic hypoparathyroidisms (digeorge syndrome, CATCH-22, Kenny-Caffey syndrome, Barakat syndrome, Kearns-Sayre syndrome, Pearson syndrome) <p>Secondary hypoparathyroidism_(maternal hyperparathyroidism)</p> <ul style="list-style-type: none"> • Iatrogenic <ol style="list-style-type: none"> 1. Use of citrate-blood products 2. Lipid infusions 3. Bicarbonate therapy 4. Loop diuretics (furosemide) 5. Phosphate therapy

hypoparathyroidism in hypomagnesemia. Electrocardiography (ECG) should be performed to assess the impact of severe hypocalcaemia on the tissue and heart, and it may reveal a QT interval, QRS and ST changes, and ventricular arrhythmia [22]. A knee x-ray is required for early childhood rickets. In case of suspicion digeorge Syndrome, chest radiography can be used to assess the presence of a thymic shadow, thus Immunological methods to determine the function of T cells in which will be abnormally reduced, in addition to the dysmorphic facial appearance, and fluorescence in situ hybridization analysis (FISH) which shows a microdeletion in chromosome 22q11.2 [23].

The therapeutic means may vary depending on the symptoms and the degree of hypocalcemia. Early-onset hypocalcaemia is generally asymptomatic and treatment should be initiated when the serum calcium level is <60 mg / L in premature babies 70 mg / L in young children [23]. 40 to 80 mg / kg / day of elemental calcium substitute will be recommended for asymptomatic newborns [24]. For infants on parenteral nutrition, calcium will be added as 10% calcium gluconate as a continuous infusion (50 mg / kg / d of elemental calcium). If

parenteral calcium is administered for more than 2 days, phosphorus should also be administered according to serum phosphate levels. In symptomatic newborns (tetany or convulsions) an intravenous infusion of 1 to 2 ml / kg / dose of 10% calcium gluconate should be administered by slow infusion over 10 minutes under cardiac monitoring. This treatment prevents severe symptoms of hypocalcemia (seizures ...), it does not normalize the calcium level. After the calcium bolus, the relay by an elemental calcium infusion of 50 to 75 mg / kg / day must be initiated [25], and a continuous bolus of calcium gluconate at 1 ml / kg / 6 hours intravenously is desirable. The calcium dosage administered should be adjusted according to the serum calcium measurement every 8 to 12 hours until the serum calcium level normalizes. The risk of severe skin necrosis secondary to extravasation of calcium during treatment with calcium gluconate intravenously is not negligible, therefore the infusion rate should not exceed 1 mg / min and monitoring of appropriate vascular access must be ensured.

Cardiac arrhythmias (bradycardia) or even cardiac arrest may develop during the infusion of calcium gluconate, where an intravenous

administration slowly for 10 to 30 minutes under cardiac monitoring should be performed. If an umbilical venous catheter is used the tip of the catheter must be strictly in the inferior vena cava to prevent hepatic necrosis.

Relay with oral calcium will be administered if patients are asymptomatic or have reached a normal serum calcium level after an intravenous infusion or presenting mild symptoms, in this case, 40 to 80 mg / kg / d of elemental calcium can be administered in 3 to 4 doses, calcium lactate, carbonate or citrate can be used. Once normocalcemia is obtained, the assessment of serum and urine calcium and creatinine levels should be done at frequent intervals and the dose should be adjusted to have daily urinary calcium excretion <4 mg / kg / day. The risk of complications such as nephrocalcinosis, renal failure and iatrogenic hypercalcemia should be avoided.

1000 to 2000 IU / d of the vitamin are recommended in case of vitamin D deficiency in case the production of active vitamin D is impaired (hypoparathyroidism or disorders of the metabolism of vitamin D), the administration of active vitamin preparations D (20 to 60 ng / kg / d of calcitriol) should be performed. The serum calcium level at the lower limit of normal must be maintained during hypoparathyroidism to avoid hypercalciuria and nephrocalcinosis. On the other hand, the treatment of pseudohypoparathyroidism must maintain a normal PTH level by keeping the serum calcium level near the upper limit of normal. In the event of hypomagnesemia, Magnesium Sulfate intravenously slowly over 2 hours (risk of cardiac arrhythmia) or intramuscularly (25 to 50 mg / kg or 0.2 to 0.4 meq / L per dose every 12 h) should be administered until the serum magnesium concentration exceeds 1.5 mg / dl (0.62 mmol / L). In the event of hyperphosphatemia, treatment aims to reduce the serum phosphate level, with a diet low in phosphate and rich in calcium with breast milk or a low phosphate formula. Calcium salts can also be used to reduce the rate of phosphatemia.

4. CONCLUSION

Hypocalcemia is the most common metabolic disorder in newborns. It is generally asymptomatic, total or ionized serum calcium levels should be monitored in at-risk neonates. The diagnostic and therapeutic management of

neonatal hypocalcemia must be initiated immediately in all infants to prevent complications and possible sequelae.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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