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Profile of Newborns with Bone Metabolic Disease in a Neonatal Intensive Therapy Unit

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Abstract

Objective: To describe the profile of newborns with BMD admitted to a neonatal intensive care unit (NICU).

Methods: This is a retrospective and documental study with a quantitative approach, performed at the NICU of a reference hospital in Fortaleza, from November 2016 to January 2017, whose sample consisted of 30 medical records. The following variables were analyzed: weight, gestational age (GI), weight / GI adequacy, gender, Apgar score, BDM associated morbidities, ventilator support, parenteral nutrition (NTP), medicines, physiotherapeutic assistance and blood biochemical analysis. The variables were analyzed by Microsoft Excel® 2016 to obtain absolute and percentage data.

Results: It was verified the predominance of extremely preterm infants, with very low birth weight, AIG, male, with scores of Apgar higher than 7, at the 1st and 5th minutes, with prevalence of respiratory distress syndrome and jaundice. Most newborns used antibiotics and tricalcium phosphate, with prolonged use of NTP. Regarding serum levels of Ca, P and FA, they were helpful in the laboratory diagnosis of this at-risk population.

Conclusion: The profile outlined in our study matches the literature reports in many aspects, revealing the importance of characterizing this group for the prognosis and short- and long-term follow-up of newborns with bone metabolic disease.

Keywords: Newborn; Neonatal Intensive Care Unit; Prematurity; Biochemical Markers

Introduction

Bone Metabolic Disease BMD is defined by changes in skeletal mineralization due to variations in bone mineral content (BMC). In the preterm newborn (PTNB) BMC is disproportionate to birth weight and gestational age (GI). In addition, reduced BM is also related to the inadequate supply of calcium (Ca) and phosphorus (P) in extra uterine life. Its pathophysiology is associated with the mineral deficiency of these substances associated with the discontinuation of the placental transport of estrogen and other hormones that promote bone construction, lack of mechanical stimuli and load on the fetal bone imposed by the muscular wall of the uterus, which fit into prematurity [1,2].

Other factors related to BMD include prolonged parenteral nutrition (NPT), jaundice, delayed introduction of enteral nutrition or its poverty in mineral content, prolonged diuretic therapy, Broncho pulmonary dysplasia (BPD), and the use of theophylline for long periods. Neonates who present this type of disorder do not exhibit a uniform clinical character, since it is possible to observe from a halt in longitudinal growth, maintenance of the cephalic perimeter, radiological signs similar to rickets, and the presence of spontaneous fractures in 10% of very low birth weight infants weight (MBP) at birth [1,2].

In the neonatal period the presence of bone fractures is very rare [3]. However, some occurrences may be recorded during delivery, such as: long bone fractures, clavicle related to shoulder dystocia, or even cranial fractures from forceps deliveries [4]. On the other hand, neonates hospitalized in Neonatal Intensive Care Units (NICUs) have a marked risk of bone fractures for a variety

of reasons including prematurity, low birth weight, malnutrition, trauma secondary to medical interventions as well as drug side effects [3-7]. In preterm NB, one of the possible causes of fracture is generally difficult to establish, and is often attributed to osteopenia of prematurity [3]. According to the literature, the incidence of fractures is very variable, ranging from 1.2 to 10.5%, being higher in very low birth weight (MBP) [3].

Therefore, BMD is among the morbidities that can directly affect the prognosis of these newborns in the short and long term, involving the most diverse organs and systems, being considered a frequent condition in premature babies, with an incidence higher than 60% in the newborn of extremely low weight (EBP) [2].

Through the tests used to diagnose BMD, biochemical markers for evaluation of bone growth and remodeling, such as hypophosphaturia and hypercalciuria that precede serum alterations (decrease of Ca and P and increase of alkaline phosphatase (FA). The most specific urinary markers are bone-specific alkaline phosphatase, deoxypyridinoline, C-terminal telopeptide of type I collagen and C-type natriuretic peptide. Moreover, the dual-absorbed X-ray densitometry, which is the standard choice for evaluating bone mineralization, with high accuracy and rigor [1].

The high incidence of BMD in newborns and the factors related to their origin and repercussion present a small number of studies on this topic. In this context, the present study is justified by filling idle gaps in the literature, in order to guide the prognosis and treatment of individuals affected by BMD. Therefore, the objective of the study was to describe the profile of newborns with BMD admitted to a neonatal intensive care unit.

Methodology

This is a retrospective and documental study with a quantitative approach, from November 2016 to January 2017 at the Neonatal Intensive Care Unit (NICU) at Hospital Geral Dr. César Cals (HGCC). The HGCC is a state tertiary reference and teaching unit in the areas of Clinical Medicine, Neonatology, Toco-Gynecology and General Surgery recognized by the MEC / MS.

The inclusion criteria were records of PTNBs diagnosed with BMD, who were hospitalized from January to August 2016 at the NICU of the HGCC, whose sample consisted of 30 records. However, damaged and readable medical records were excluded, incomplete records referring to the study variables.

Variables analyzed: weight, GI, weight adequacy / GI, gender, Apgar score, BMD associated morbidities (respiratory distress syndrome, jaundice, BPD), use of ventilatory support such as invasive mechanical ventilation (IMV) (CPAP) and oxygen therapy, time of (NPT), medicines use, physiotherapeutic assistance and blood biochemical analysis (Ca, P, and FA).

The data were tabulated using the Microsoft Excel® 2016 program to obtain absolute and percentage data. The study was approved by the Research Ethics Committee of the Escola de Saúde Pública do Ceará, through opinion 1773571 and the Research Ethics Committee of the HGCC under opinion 1821727.

Results and Discussion

Table 1 shows a predominance of very low birth weight infants and GI infants. Regarding the weight / GI adequacy, there was a preponderance of NBs, suitable for gestational age and males. In relation to Apgar in the 1st and 5th minutes, values above 7 were observed.

		Frequency		
Variables	**n**		**%**	**Standard of analysis**
Weight at birth (g)				
Low weight	4		13,3	Lower than 2.500 g
Very Low Weight	17		56,6	Lower than 1.500 g
Extreme Low Weight	9		30,0	Lower than 1.000 g
Gestational Age (Weeks)				
Bordering	1		3,3	35 and 36 weeks
Moderate	11		36,6	31 and 34 weeks
Extreme	18		60,0	Lower than 30 weeks
Weight Adequacy /IG				
Suitable for gestational age	22		73,3	Curve at about 10 e 90 percentile
Small for gestational age	7		23,3	Lower curve than 10 percentile
Great for gestational age	1		3,3	Curve higher than 90 percentile

Gender				
Male	17		56,6	-
Female	13		43,3	-
Apgar 1ª minute				
≥ 7	15		53,5	-
< 7	13		46,4	-
Apgar 5ª minute				
≥ 7	26		92,8	-
< 7	2		7,1	-

Table 1: Characterization of newborns at birth in the HGCC. Fortaleza / CE

In Table 2, it was verified that most NBs used non-invasive ventilatory support. According to nutritional support, most NBs used NPT with an average of 10 to 20 days. Through the most used medicines, the antibiotic and tricalcium phosphate prevailed. In conjunction with the classic therapy, physiotherapeutic assistance, both respiratory and motor. Regarding the morbidities related to the onset of BMD, we highlight: RDS, jaundice and BPD.

		Frequency	
Variables	**n**		**%**
Ventilation Support			
O_2 circulating	3		10
Oxihood	18		60
VMI*	19		63,3
CPAP**	25		83,3
Parenteral Nutrition			
≤ 10 Days	11		42,3
11 à 20 days	11		42,3
↑21 days	4		15,3
Medicines			
Tricálcico Phosphate	25		83,3
Antibiotics	25		83,3
Surfactant	14		51,8
Diuretics	9		30,0
Physiotherapeutic Assistance			
Motora	26		86,6
Respiratory	26		86,6
Morbidity			
SDR	29		96,6
Jaundice	26		86,6
Bronchopulmonary dysplasia	4		13,3

Table 2: Assistive characterization of newborns with bone metabolic disease in the HGCC, Fortaleza/CE, 2016. **Subtitle**: VMI - Mechanical Invasive Ventilation; CPAP - Continuous Positive Airway Pressure. SDR - Respiratory distress syndrome

Table 3 addresses the serum biochemical parameters of Ca, P and FA, where Ca levels are elevated in 53.3%, while P values remained within the normal range. The values of AF were significantly higher than 600 UL in 96.6% (n = 29) of PTNB, a value considered suggestive of BMD.

In view of the diversity of studies that describe the profile of newborns hospitalized in NICUs identifying the risk factors and characterizing them with emphasis on prematurity, low birth weight, presence of congenital malformation and Apgar in the fifth minute lower than seven, as predictors of the morbidities that affect them [8], it is important to characterize newborns with BMD admitted to the NICU.

		Frequency		
Variables	**n**		**%**	**Reference values**
Calcium (Ca)				8,5 a 10,2 mg/dL
↑10,2 mg/dL	16		53,3	-
8,5 à 10,2 mg/dL	11		36,6	-
↓ 8,5 mg/dL	3		10	-
Phosphor (P)				2,5 a 5,6 mg/dL
↑5,6 mg/dL	4		23,5	-
2,5 à 5,6 mg/dL	9		52,9	-
↓ 2,5 mg/dL	4		23,5	-
Alkaline phosphatase (FA)				150 a 600 U/L
↑ 600 UL	29		96,6	-
150 a 600 U/L	1		3,33	-
↓ 150 U/L	-		-	-

Table 3: Main biochemical markers of newborns associated with bone metabolic disease in the HGCC. Fortaleza/CE, 2016

In view of the diversity of studies that describe the profile of newborns hospitalized in NICUs identifying the risk factors and characterizing them with emphasis on prematurity, low birth weight, presence of congenital malformation and Apgar in the fifth minute lower than seven, as predictors of the morbidities that affect them [8], it is important to characterize newborns with BMD admitted to the NICU.

Growth is a continuous and complex path that results from the sum of several factors, such as genetic, nutritional, hormonal and environmental factors. Through those factors predisposing to BMD impairment, the following stand out: weight and GI [9,10].

In this context, the present study evidenced the prevalence of 56.6% of the very low birth weight infants (VLBW), as shown in Table 1. This characteristic can influence in the short and long term the structural development of this population. Although it is still difficult to predict the growth process of a VLBWI, they may present relevant clinical intercurrences, leading to energy expenditure and serious restrictions in the supply and utilization of nutrients [9].

Lotfi *et al* (2014) [10] developed a study comparing the effects of nutritional formulas on VLBWM with BMD, it was observed that newborns weighing less than 1,200g developed rickets early compared to those weighing more than 1,200g.

The development of BMD usually occurs around 6^{th} to 12^{th} after birth. Mostly, the infants are only able to reach BMC and bone mineral density after six months of corrected age (CI) [1,11]. Thus, according to the present study, we observed that there was a predominance of 60% of extreme PTNB diagnosed with BMD, suggesting that this population with GI less than 30 weeks are more vulnerable to this morbidity.

Rover (2016) the relationship between weight / GI as a variable that induces changes in growth [12], especially in VLBW infants during their hospital stay and during the first year of life, mainly affecting small infants for gestational age (SGA). When comparing with the current research profile, the prevalence of suitable newborns for gestational age was observed, according to Table 1, as a result of Rover's findings (2016).

Regarding gender, the prevalence of male neonates in relation to females is highlighted in the present investigation. Similar results were found in the literature [13]. The protective factor of the female gender is attributed to the maturation of the systems and organs that occurs in a way, but quick when compared to the male gender that presents slowly during the fetal growth, causing a greater fragility [14]. On the other hand, some studies suggest that the male gender presents a lower speed in the global maturation in relation to the female, due to the influences of the Y chromosome, contributing to the appearance of morbidities [15].

Through the pathologies that predispose to the occurrence of BMD, some studies point out that BPD, necrotizing enterecolitis and jaundice are some of the pathologies that are associated with its development and are usually intercurrences specific to PTNB [1,2,13]. In the present study there was a prevalence of RDS and jaundice as more frequent morbidities, according to Table 2. In contrast, in the study by Lotif *et al* (2016) [10], the postnatal complication correlated with the onset of BMD was peri-intraventricular haemorrhage (HIVV), a result that was inconsistent with our findings.

Based on the care practices that cause a differential in the clinical outcome of the newborns, and especially of the PTNBs, there is a need for advanced neonatal resuscitation procedures, defined as intubation and / or cardiac massage and / or use of medications in the birth room [16]. Therefore, authors report that the extrauterine growth is influenced when there is a need for ventilatory assistance on the first day of life and use of ventilatory support for long periods during the hospitalization period.

The current study demonstrates that most of the neonates remained on noninvasive ventilation under the CPAP modality. The effectiveness of this modality is due to the provision of continuous positive airway pressure, facilitating the opening and stabilization of these routes, favoring the reduction of resistance and respiratory effort in RNPT. This therapeutic strategy has been preferred in this population due to the few complications related to its use [17].

Other factors are worth mentioning because they are associated with the onset of BMD, such as the NPT over 4 weeks, the mineral deficiency in enteral nutrition, its late onset, and the use of medicine such as diuretics and corticosteroids are pointed by some authors as factors related to this metabolic disorder [2,10].

The duration of NPT observed in the current study was at about 10 to 20 days, a result that corroborates the findings of Lotfi *et al* [10]. In the same study the TPN time was shorter than 4 weeks, where this result had no direct effect on BMD, but the beginning of the introduction of oral diet was at about 1 to 90 days, which according to the studies later this introduction , the greater the probability of radiological alterations in the bone growth of these children.

In addition to the use of TPN, the PTNB may have as influential postmortem factor in BMD the use of drugs necessary to stabilize the clinical condition during the NICU stay. The literature indicates that the use of diuretics, amphotericin, corticosteroids and methylxanthines may lead to renal [18]. When analyzing the data of this research, it was noticed that there was a prevalence of the use of antibiotics and diuretics, according to Table 2, which corroborate with findings of the literature.

In addition to these substances predisposing to BMD, studies show that in some services tricalcium phosphate is used in the treatment of this metabolic disorder, when it becomes impracticable to use a fortifier in breast milk or when PTNB has already adapted to the complete diet of the breast [15]. The current research shows that 83.3% of the babies used tricalcium phosphate in the treatment of this morbidity, as shown in Table 2.

In view of the potential risk of BMD and its consequences, the conventional therapeutic methods mentioned above combined with physical therapy lead to a decrease in the predominant bone mineral depletion in the first weeks of life of premature infants [2]. Therefore, as a prophylaxis of BMD, some studies indicate that motor physical therapy through passive exercises in the first week of life attenuates bone loss, in extreme PTNB with birth weight on average of 1,135g [18].

To understand the consequences of BMD, it is necessary to know its pathophysiology of PTNBs, in which P deficiency. This hypophosphatemia together with hypercalcemia and vitamin D deficiency due to the insufficient time required to transport it during pregnancy, predisposes to the onset of this metabolic disorder [10,11,18].

According to the study by Margotto (2013) [18], the biochemical diagnosis is performed through the analysis of serum and urinary levels of Ca, P, and FA. Based on the analysis of these minerals, the literature shows that serum Ca in BMD is usually within or below the normal range (8-11mg / dL), whereas P is considered to be a serum level lower than 5.6mg / dL as a risk factor for the development of this metabolic disorder [10,18].

In literature, the most frequent reference values are AF. A study performed at a university hospital in São Paulo used as cutoff values for the diagnosis of osteopenia 300 and 1,200 IU / L [1]. In the present study, the reference value used at the study site was 150 to 600 U / L, thus observing high rates of serum AF levels in the population analyzed, as shown in Table 3.

In the case of serum Ca and P values, the present study observed a slight alteration in serum Ca rates compared with studies already performed [10]. Thus, serum P levels were considered normal in most of the population according to reference values found in Table 3.

Conclusion

The profile of the neonates in the present study was characterized by extremely low birth weight preterm infants, suitable for gestational age, with an emphasis on males and Apgar scores above 7, at 1 and 5 minutes, with prevalence of RDS and jaundice. Other factors were relevant for the diagnosis of BMD, such as prolonged use of NTP, antibiotics and tricalcium phosphate. Regarding the serum levels of Ca, P and FA were supportive in the laboratorial diagnosis of this population.

It is concluded that the profile outlined in our study matches the literature reports in many aspects, revealing the importance of the characterization of this risk group for the prognosis and short- and long-term follow-up of newborns with bone metabolic disease.

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