Metabolic bone disease of prematurity – an overview

Srinivas Nallagonda
Madhavi Nallagonda
Anjum Deorukhkar

Abstract

With improved survival of extreme preterm and very low birth weight infants, there has been an increased incidence of metabolic bone disease (MBD). The last couple of decades have seen better awareness of the condition which in turn has led to improvement in the management and prevention of MBD. MBD occurs because there is difficulty in matching intrauterine mineral accretion rate after birth. The lack of a single specific and sensitive diagnostic test frustrates early diagnosis in many babies. Investigations like dual energy X-ray absorptiometry (DEXA) and quantitative ultrasound scanning are helpful in establishing a diagnosis but currently used mostly in research studies. A pragmatic approach for paediatricians is to pre-empt the formal diagnosis and supplement those at risk with adequate minerals and vitamin D, whilst monitoring the blood markers of MBD. Despite the noticeable short-term complications and stunting effect on childhood height, the prognosis of MBD is generally good. The aim of this article is to provide the reader with an improved understanding of the aetiopathogenesis, and offer some practical guidance on when and how to investigate and manage the metabolic bone disease of prematurity.

Keywords alkaline phosphatase; DEXA; metabolic bone disease; osteopenia; prematurity

Introduction

Survival rates of the extreme preterm infants have increased with advances in neonatal intensive care over the last century. Optimal care of these babies requires careful treatment of all potential morbidities. These infants remain at a significant risk after birth of metabolic bone disease (MBD). This is principally as a result of post-natal nutrition being unable to match the intrauterine mineral delivery and accretion rate in the last trimester when the human fetus acquires the majority of its bodily minerals.

In addition to inadequate mineral supply there may be other factors that play role in MBD including chronic illness, immature gut, hormonal imbalance and use of medications like diuretics and steroids. MBD is not likely to be clinically apparent until late in the disease process as clinical features are dependent upon lack of growth. The clinical onset therefore varies between three to twelve weeks. In most cases the abnormal biochemistry becomes evident before the appearance of radiological signs. The radiological features include osteopenia, evidence of rickets and fractures.

Incidence

Different terms have been and are still used in the literature for MBD, such as osteopenia of prematurity, neonatal rickets and rickets of prematurity. The prevalence of the MBD varies with gestational age, birth weight, feeding practices and co-morbidities. This also varies according to the precise definition of MBD used, based on whether the radiological features or biochemical markers are taken into consideration. Some of the literature has quoted the incidence of the MBD as being as high as 55% of infants born with birth weight less than 1000 grams and 23% of infants weighing less than 1500 grams at birth.

Studies from the late 1980s highlighted the importance of this emerging problem. One showed that in 48 infants of birth weight less than 1000 grams who survived for more than 28 days only one quarter (25%) had normal X-rays throughout. 10 infants (21%) showed osteopenia and 26 infants (54%) had classical changes of rickets. Eight infants had spontaneous fractures. There was poor correlation between peak values of serum alkaline phosphatase (ALP) and the radiological changes. Subsequent observational studies have confirmed that the incidence is inversely related to the gestational age and is consistently more common in exclusively breast fed preterm infants compared to preterm infants who are fed with fortified milk formulas.

Aetiology

Fetal bone mineralisation predominantly occurs in the third trimester with 80% of calcium and phosphate mineral accretion taking place during this time. Infants born prematurely are therefore primarily deficient in the mineral resources. The *in utero* mineral accretion rate is difficult to match with the post-natal supplementation alone. Postnatal supplementation has various limiting factors in the form of stability of parenteral nutrition with extra mineral supplements, delay in starting of milk feeds, absorption and bioavailability of oral mineral supplements. Additionally, other co-morbidities like diuretic or steroid usage in chronic lung disease or long periods of gut rest for various medical reasons will adversely affect the mineral accretion. The role of vitamin D in MBD remains contested but is hot topic in current literature. Further evidence is required to find out if inadequate levels of vitamin D contribute significantly to MBD.

Risk factors

The known risk factors for MBD are summarised in Box 1. Many are overlapping and it is impossible to completely disentangle

Srinivas Nallagonda *MBBS DCH DNB in Paediatrics (Master degree) India, MRCPCH FRCPCH is a Consultant in Neonatal Medicine in the Tertiary Neonatal Intensive Care Unit, Luton & Dunstable University Teaching Hospital NHS Foundation Trust, Luton, UK. Conflict of interest: none.*

Madhavi Nallagonda *MBBS MRCP is a Specialty Registrar in Chemical Pathology and Metabolic Medicine, Leicester Royal Infirmary, Leicester, UK. Conflict of interest: none.*

Anjum Deorukhkar *MBBS DCH (Mumbai) MD (Paed) MRCP (Edinburgh) DCH (London) MRCPCH is a Consultant Neonatologist with Nottingham University Hospitals NHS Trust, and Hon. Lecturer School of Nursing and Midwifery, University of Sheffield, UK. Conflict of interest: none.*

Established risk factors for MBD

Extreme prematurity
Birth weight less than 1500 grams
Predominantly breast fed infants
Use of loop diuretics (e.g. furosemide)
Steroid usage
Methylxanthine administration (e.g. caffeine)
Enterocolitis
Bronchopulmonary dysplasia
Delay in establishing enteral feeds
Prolonged parenteral nutrition
Cholestatic jaundice
Short gut
Lack of mechanical stimulation
Poor maternal nutrition
Sepsis
Acidosis
Cerebral pathology
Neuromuscular conditions

Box 1

them from each other. For instance, children with bronchopulmonary dysplasia are more likely to receive treatment with diuretics and steroids.

Pathophysiology

Majority of the body calcium (Ca) and phosphate (P) are stored in the bone microcrystalline hydroxyapatite. The apatite of bone formation requires availability of minerals in adequate quantities. The homeostasis of minerals is critically important for bone formation. This homeostasis depends on function of hormones, dietary intake of minerals, gut absorption, bone accretion, kidney reabsorption and urinary excretion.

Bone development *in utero* is most rapid in the third trimester and adequate mineral availability is essential for this process. The third trimester mineral accretion rate for Ca is 100–120 mg/kg/day and phosphate is 50–65 mg/kg/day which equates to approximately 20 grams of Ca and 10 grams of P in the last three months of intrauterine life.

The central role of the placenta in bone mineralisation

Calcium is actively transported across the placenta by calcium pumps in the basal membrane of the placenta which result in a maternal: fetal transplacental Ca gradient of 1:4. The placenta is also able to convert the 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol, which assists transfer of phosphate to the fetus.

Fetuses who are growth restricted due to chronic placental dysfunction may be osteopenic due to disruption of calcium or phosphate transport. Demineralisation is also observed in infants born to mother with placental infection and chorioamnionitis.

Postnatal adaptation

Soon after birth, with ligation of the umbilical cord the mineral and nutrient supply to the newborn is cut off. The continuing demand of bone for Ca leads to rapid fall in serum Ca level. The low serum Ca level leads to stimulation of PTH secretion but the response of the parathyroid gland to the falling Ca levels is blunted in the first forty eight hours of life.

Multiple factors affect Ca absorption such as solubility and bioavailability, quantity and quality of Ca, gut function and vitamin D status. Ca absorption from the gut occurs both passively and also actively by vitamin D dependent transport. The gut absorption in premature newborn baby is not very efficient. This, in combination with low mineral content of the human milk leads to net reduction of Ca and P supply. P supply regulates Ca absorption and retention. The high P level in the diet helps the Ca absorption and retention. Mineral retention sharply falls after birth. The skeletal growth remains high which will lead to reduced bone density. The physical activity is beneficial to mineral accretion. The immobility of sick preterm babies in incubator does not promote bone mineral accretion. Drugs such as steroids, diuretics and caffeine stimulate osteoclast activation which will lead to osteopenia.

Diagnosis and monitoring

Diagnosis of MBD is usually based on serum analysis, radiological findings and clinical features. MBD may not be clinically obvious until it is very severe. Similarly radiological findings also delayed compared to biochemistry. Hence early diagnosis mostly depends on the combination of biochemistry tests (see Box 2). Clinically MBD presents as enlargement of anterior fontanelle, widening of skull sutures, frontal bossing, craniotabes, thickening of costo-chondral junctions, wrist joints and fractures of ribs and long bones. Radiological examination shows osteopenia, enlargement of the epiphysis, irregular border between growth cartilage and metaphysis. Fractures and softening of ribs may also be evident in more advanced cases.

Serum calcium level is usually well maintained within normal levels due to the effect of PTH on the bones. Serum phosphate correlates well with MBD and it is highly specific. However the test is not sensitive enough to identify the preterm infants with MBD. Serum alkaline phosphatase (ALP) is a marker for the bone turnover. MBD is characterised by low serum phosphate and elevated ALP levels. Serum ALP levels higher than 900 IU/l associated with a serum phosphate level lower than 1.8 mmol/l have a diagnostic sensitivity of 100% and specificity of 70% for MBD.

Biochemical markers of MBD

Serum alkaline phosphatase
Serum phosphate (P)
Serum calcium (Ca)
Serum parathyroid hormone
Vitamin D assay
Urinary Ca and P
Percentage of renal tubular reabsorption of phosphate (TRP)*
*The following equation is used to calculate the TRP:
TRP% = (1 − (urine phosphate/urinary creatinine) × (plasma creatinine/plasma phosphate)) × 100.
NB. All units must be the same (mmol/L) therefore, divide serum creatinine (μmol/L) by 1000.

Box 2