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Trends in Management of Osteopenia in Neonates: A Review

Medical Science

KEYWORDS : Dual-Energy X-ray absorptiometry (DXA), Metabolic bone disease of the prematurity (MBD), Bone mineral density (BMD)

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ABSTRACT

Neonatal osteopenia is common preventable condition that predisposes to pathological fractures in neonates. Commonest cause of neonatal. Osteopenia is deficiency of minerals and subnormal bone formation.

Preterm infants are at increased risk of developing this condition. Other causes of neonatal osteopenia are inadequate mineral supplementation prolonged parenteral nutrition, chronic diseases such as bronchopulmonary dysplasia and shortbowel syndrome . Prompt identification of this condition is very necessory. Various markers help in early detection and treatment in high-risk populations .Investigations like photon emission absorptiometry ,quantitave ultrasounds are usefull methods of early detection of this condition. But dual-energy X-ray absorptiometry (DXA) is preferred radiological method method of early detection. Conventional use of serum biochemical markers such as calcium, phosphate, alkaline phosphatase and osteocalcin also help in prompt detection of Osteopenia of neonates. Prevention and early detection of osteopenia is the key to the successful management of this condition in neonates.

Introduction

The ongoing scientific advancement in preterm neonatal care has resulted in sensible decline in mortality in premature babies. The neonatal mortality has fallen in a expectant way with an observational fall in last few years. The survival is inversely proportional to gestational age of the neonate. However, better survival rate attained because of efficient, intensive, newborn care does not always result in a disease free infant .

Oflate many workers are shifting their focus on osteopenia of prematurity. This condition is also called by name of metabolic bone disease of the prematurity (MBD) .It is caused by many nutritional and biochemical factors finally leading to a decrease in bone mineral content. It may be or may not be associated with bony deformities or features of rickets.

The pathogenesis of osteopenia is because of insufficient supply of essential nutrients (vitamin D, calcium and phosphorus), a longer duration of total parenteral nutrition(TPN), decreased mobility and use of certain drugs .The osteopenia normally surfaces by two to three months of age However it may be undetected till severe demineralization (a reduction of BMD of 20 – 40%) occurs.

The Evaluation of bone mineral density (BMD) is garnering huge attention amongst neonatologists(Neonatal Research Network 2004).Bone density strongly determines strength of bone . Factors like low bone mineralization or high resorption can lead to fall in BMD . Factors that cause increased risk of osteopenia in neonates are, depressed opportunity for transplacental calcium transport as in in premature babies, poor nutritional intake. The incidence of MBD in newborn infants is highest in lowest gestation and birthweight. Nearly one third of extremely low birth weight babies suffer from MBD or osteopenia(Demarini S 2005). Other contributing factors which cause MBD are necrotising enterocolitis(NEC) ,Chronic lung disease , late establishment of full enteral feeds and babies on longer duration of TPN(Abrams AS 2007).

Pathophysiology

During the period of 12 to 20 weeks gestation, fetal serum levels of calcium and phosphate are 120% as compared to the levels in the mother(Rigo J & Senterre J,2006). However Bone mineralization primarily happens during the third trimester. When this high fetal requirement is not being supplied then subnormal fetal bone mineralisation may result (Heaney RP & Skillman TG ,1971).Vitamin D is transported across placenta mainly as 25-hydroxyvitamin D and later on it is changed to 1,25-(OH)2 Vit D within the kidney of fetus . However, the real work of 1,25- (OH)2 Vit D in bone mineralization of fetus is not completely understood. It is also well known that chronic maternal vitamin D deficiency could hamper fetal skeletal development(Rigo J & De Curtis M, 2006).The fetal accretion of calcium and phosphate during the last three months of gestation is about 20 g and 10 g respectively, which symbolizes accumalation rates of 120mg/kg/day and 60 mg/kg/day calcium and phosphate respectively(Rigo J 2006).

A very important role in skeletal accretion of the fetus is played by the placenta. The calcium active pump present at the basal layer pushes the ions in to the fetal side maintaining a gradient of 1:4 .Moreover, the placenta is able to convert vitamin D to 1,25-dihydrocholecalciferol which is essential for mobilizing phosphate to the fetus(Rigo J 2006).Therefore, Babies born before term will not be sufficed with fetal transport of calcium and phosphorus and this affects bone mineralization. The diseases of placenta like placental insufficiency decrease the calcium and phosphate movement across it; which is why neonates with intrauterine growth restriction may suffer from demineralization. Other conditions which cause demineralization are chorioamnionitis and placental infection . A study showed that supplementation of calcium (2 g from before 22 weeks of gestation) to mothers with decreased dietary calcium intake was successful in increasing bone mineral content (BMC) of babies born at term. In the initial half of infancy Marrow cavity grows faster when compared to the cortex and the bone density could fall by nearly one third. Premature babies have less cortical growth with a subsequent fall in bone strength (Litmanovitz I, Dolfin T & Regev R, 2004)

Risk Factors

As discussed , prematurity is a very significant risk factor for neonatal osteopenia since calcium and phosphorus transport across the placenta is highest after second half of pregnancy to almost 60-70% of accretion of calcium occurring during this time (Sparks JW 1984). So, premature babies have inadequate bone mineral stores at birth that are required for post natal rapid bon(Schultheis L 1991). The association between decreased bone mineral density and decreased spontaneous body movements has been demonstrated in a study using quantitative ul-

trasound assessment in babies with developmental anomaly of brain (Eliakim A, Nemet D, Friedland O, Dolfin T & Regev RH ,2002). Babies with low levels of physical activities such as in preterm babies are at increased risk of developing osteopenia (Moyer-Mileur L, Luetkemeier M, Boomer L & Chan GM, 1995). long-term use of certain medications such as methylxanthines and diuretics such as frusemide can increase urinary loss of calcium which is required for bone mineralization(Zanardo V, Dani C &Trevisanuto D , 1995). High-dose systemic steroids inhibits osteoblast function and DNA synthesis , but this effect is reversible. Neonatal osteopenia is also associated with infection(Colwell A & Eastell R,1996).This is due to increased baby's catabolic state during infection.

Radiological Investigations

Radiographic evidences of low bone mineral content are often late as it takes atleast 40 percent of demineralization to be detected by Xrays (Mazess RB, Peppler WW, Chesney RW, Lange TA, Lindgren U & Smith E Jr ,1984). Today the preferred investigation to study bone mineral density in the adults is dual-energy X-ray absorptiometry (DXA).A DXA investigation uses two X-ray beams of varying energy levels to study the patient. Various body tissues have different absorption capacity as for as x ray beam absorption is concerned. The tissues enjoy specific differential absorption in fixed area of projection. So when we focus on tissues with known density we can use scanner to study bone mineral content which can be calculated with the formulae BMC/Ap.

Although investigations like single photon emission absorptiometry correlate well with BMC, DXA has been shown to be superior to it as absorptiometry does not correlate well with fracture risk and rickets. DXA, on the other hand, has been shown to correlate well with fracture risk (Syed Z & Khan A,2002). Rigo et al has shown that DXA is a good modality of estimation BMC in both preterm and term infants(Katzman DK, Bachrach LK, Carter DR,&Marcus R ,1991). There are certain mathematical conversions based on assumptions of the skeletal structures of different bony regions which are needed to be applied to preterm babies . DXA exposes the babies to less ionizing radiation as compared to a chest radiograph .A New portable less invasive and inexpensive is the quantitative ultrasound (QUS).Herein the speed of sound is used to assess the BMD dimensions. It has been shown that QUS measurements can be adequately correlated with bone density and structure (Gluer CC, Wu CY, Jergas M, Goldstein SA &Genant HK,1994), but not with the thickness of the bony cortex and QUS can be practical noninvasive method of studying for osteopenia in premature babies (Rubinacci A, Moro GE, Boehm G, De Terlizzi F, Moro GL & Cadossi R ,2003).

Biomarkers

By convention various serum markers are used to diagnose the MBD in newborn infants. They Include measurement of calcium, phosphate, alkaline phosphatase and osteocalcin are measured(Abrams AS 2007), But these biomarkers suffer from certain limitations(Hung YL, Chen PC, Jeng SF, Hsieh CJ, Peng SS & Yen RF, 2011). Although serum phosphate concentration reflect bony phosphorus levels well, serum calcium concentration are not depictive of the same as it is maintained at the expense of bone calcium content. And also the serum calcium is affected by other non bone conditions (Lyon AJ, McIntosh N, Wheeler K & Brooke OG ,1984). Serum alkaline phosphatase levels are depictive of turnover of bone metabolism. These levels are directly associated with the degree of cellularity of the bone .Serum alkaline phospatase levelsmore than 700 IU/L, are predictive of severe neonatal MBD. This raise of serum levels may occur before the onset of clinical symptoms(Lyon AJ,1984). Bone-specific alkaline phosphatase, an enzyme which is present in osteoblasts is more specific biomarker of turnover of bone(Faerk J, Peitersen B, Petersen S & Michaelsen KF ,2002) Another biomarker called Osteocalcin also represents activity of the osteoblasts, however this does not strongly correlate to the degree of MBD in neonates (Eastell R, Colwell A, Hampton L & Reeve J, 1997). It is always better to prevent than to treat osteopenia and it is often tough to manage this condition. The main cause for raise in the risk of MBD in newborn babies on TPN is the low solubility of calcium and phosphate elements within these solutions. Hence all parenteral solutions may not suffice the metabolic demands of growing premature babies(Koo WW,1992) The requirements of newborn are different during the different times of postnatal period. Usually calcium supplementation by 1 mmol/kg/day is adequate for metabolic need of newborn in the initial days of neonatal life. Increasing growth and mineralization of bone after this period makes the calcium and phosphate requirement to increase. A randomised controlled trial showed that by raising calcium and phosphorous supplementation in TPN solutions from 0.68 to1.25 mmol/kg/day and 0.61 to 1.20 mmol/kg/day, respectively in premature neonates resulted in higher plasma phosphate levels , decreased activity of plasma alkaline phosphatase , and decreased X ray evidence of rickets(MacMahon P, Blair ME, Treweeke P & Kovar IZ ,1984).

Absolute Calcium and phosphorus concentrations in TPN solutions and their relative concentrations with respect to each other both decide the retention rates in the body(Atkinson S &Tsang RC ,2005). Other studies have also deduced that when TPN solutions provide calcium and phosphorus supplementation at the rate of 1.45 to 1.9 mmol/kg/day and 1.23 to 1.74 mmol/kg/day respectively could help in achieving mineral retention rates up to the tune of 94% and 97% respectively(Rigo J, Pieltain C, Salle B & Senterre J,2007).Interestingly ,In a study which observed the varying ratios of calcium to phosphorus in TPN solutions from 4:1 to 1:8 by weight, and their retention in the body, it could be recognized that calcium and phosphorus retention was highest when it was in between 1.3:1 to 1.7:1.54. Another captivating finding was that when the balance falls below 1:1 it may result in hypocalcaemia and hyperphosphataemia (Vileisis RA ,1987) .

Studies which infused calcium and phosphate separately reported decreased retention rates of between 42 and 63%56,57 as compared to 83 to 97% achieved with conventional simultaneous infusions (Vileisis RA ,1987) . Moreover, separate infusions are associated with hypercalcaemia and hyperphosphataemia and may increase parathyroid hormones VLBW babies frequently suffer from feed intolerance and have high energy and mineral requirements, but enteral supply of calcium and phosphorus is often limited. This inadequacy of the mineral supply gets manifested in to raised alkaline phosphatase and 1,25 (OH) Vit D levels, manifestation of X-ray features of rickets(Lyon AJ, McIntosh N, Wheeler K & Williams JE,1987), and decreased Bone mineral content. Preterm babies can get a nearly two thirds of calcium requirement from breast milk.

Phosphorus content has its bearing on retention of calcium within the body . So combining calcium with phosphate helps in better absorption. When calcium alone is added to milk the rate of absorption of calcium is 35 mg/kg/day .When both calcium and phosphorus are supplemented to the milk absorption is nearly 60 mg/kg/day(Salle BL, Senterre J & Putet G,1993). Better accretion of calcium and phosphorus can be attained by supplementation of mother's milk with calcium and phosphate salts at the dosage of 3.7-5.8 mmol/kg/day and 2.5-4.1 mmol/kg/day (Holland PC, Wilkinson AR, Diez J & Lindsell DR,1990) .An interesting study advocated regular exercise regime for higher raise in body weight, length ,area, mineral content of Bone and lean body mass (Moyer-Mileur LJ, Brunstetter V, McNaught TP, Gill G & Chan GM,2000). Another study by Litmanovitz et al demonstrated favorable effects of a exercise schedule on bone

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mineral density when calculated by QUS(Litmanovitz I, Dolfin T, Friedland O ,2003)

Prematurity and its effect on Adult BMD

There is nearly unequivocal data on the long-term effects of preterm birth on the bones and its risk significance in causation of osteopenia when compared with term babies. At Term corrected gestational age ,the preterm neonates have a decreased bone mass (J. De Schepper, F. Cools, Y. Vandenplas & O. Louis,2005) and Bone mineral density (I. Ahmad, D. Nemet &A. Eliakim 2010). Moreover an observational study in boys of 7-year age demonstrated higher quantification of whole body mineral content , BMD of hip joint ,bone cortical thickness, and in term boys in comparison with premature boys after adjusting for weight, height and age (H. Abou Samra, D. Stevens, T. Binkley & B. Specker, 2010) Analogously an thought-provoking study (M. S. Fewtrell, A. Prentice, T. J. Cole& A. Lucas ,2010)revealed that former preterm neonates who were followed up for ten years it was found that they were lighter and had lower bone mineral density in comparison to term control group. Most probably these deficiencies continue to stay in to puberty and adolescence. Backström et al (2005) demonstrated that subjects in there adulthood , who were former preterms, when assessed with computerized tomography had less bone strength at the distal tibia and radius in comparison with controls who were matched .

Conclusions

Neonatal osteopenia occurs commonly in preterm infants, babies on long-term diuretics or corticosteroids, and those with inadequate nutritional supplementation. It is important for us to manage such high-risk babies to regularly monitor biochemical markers for evidence of impaired bone mineralization. DXA is gaining importance as a preferred noninvasive mode of detection of BMD. Prevention and early detection of osteopenia is the key to the successful management of this condition in premature babies. Such neonates should be started on oral calcium phosphate supplements as soon as they achieve full feeds..

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