RESEARCH ARTICLE

Maternal vitamin deficiencies causing bone disorders and fractures in infants

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Abstract
Recent publications have again drawn attention to long bone fractures in newborn infants with severe vitamin D deficiency due to maternal subnutrition. This is a reminder of the complete dependence of an infant on maternal nutrition; the bones that fracture in early infancy are formed during gestation.

This review covers previous reports of congenital rickets including the difficulties in diagnosis, not least because there may be none of the usual radiological hallmarks of rickets. It also outlines ways of making a retrospective diagnosis of vitamin D deficiency after the infant's biochemical findings have become normal.

It is likely that similar considerations apply to vitamin C deficiency. Although overt scurvy is uncommon it is clear that vitamin C subnutrition is widespread even in Western countries. Vitamin C has many roles but among them is its requirement in the formation of collagen. Thus it is not surprising that fractures and intracranial bleeding are well-recognised features of vitamin C deficiency.

Maternal subnutrition of vitamin D and vitamin C are important conditions in the wide differential diagnosis of unexplained fractures and fracture-like lesions in infancy.

Keywords: Rickets, Scurvy, Vitamin D deficiency, Vitamin C deficiency , Fractures, Non-accidental injury, Classical metaphyseal lesions, Congenital vitamin deficiencies

1. Introduction

A recent report from France of two newborn infants with long bone fractures and severe vitamin D deficiency has again drawn attention to the complete dependence of an infant on maternal nutrition.[1] In that report it was striking that neither child had any of the conventional radiological features of rickets. Nor did either have the biochemical abnormalities associated with rickets other than the very low serum 25-hydroxyvitamin D (25OHD) levels.

This paper summarises the evidence that maternal subnutrition needs to be included in the differential diagnosis of unexplained fractures in infancy. It also outlines the practical measures required to ensure an accurate diagnosis in individual cases.

2. Vitamin D deficiency

Numerous publications in recent years have shown that deficiency of vitamin D is widespread. While there is still uncertainty about the 25OHD level that should be regarded as important, it is clear that significant deficiency is common by any standards. This is true in different age groups and in many parts of the world including Europe and North America.[2,3]

Vitamin D status in mothers and their infants has been explored in numerous studies.[4,5] Many of the factors influencing maternal nutrition are already identified. The 25OHD levels in cord blood or in neonates generally mirror those of the mothers.[6,7,8] However some infants whose mothers were particularly deficient have exceptionally low values.[9]

It is clear that maternal deficiency has consequences for the child. These include intrauterine growth restriction, preterm labour, positional skull deformation, hypocalcemic seizures and lung problems in preterms.[10-14] There is a wide consensus advocating vitamin D supplementation of women in pregnancy.[15,16]

One unsurprising consequence of maternal vitamin D deficiency is frank rickets in the child. We have summarised 25 reported cases with clinical features of rickets identified within two weeks of birth including five with fractures. The incidence of fractures was probably an underestimate in that not all the patients had skeletal surveys; asymptomatic fractures, particularly of the ribs, may not have been detected. In 16 cases the diagnosis of rickets in the child led to the identification of symptomatic osteomalacia in the mother.[17] Others have reported similar findings.[18]

2.1 Vitamin D deficiency and fractures

Fractures have been recognised as a consequence of rickets for many years. In 35 reported cases of children under the age of two years there were 58 long bone fractures and at least 40 rib fractures. Most of the long bone fractures were undisplaced, most were asymptomatic and most were apparently spontaneous.[19] Rickets has been identified as the most likely cause of fractures in reports of patients initially thought to have been abused.[20,21] Others have drawn attention to the dangers of failing to recognise vitamin D deficiency as an important cause of fractures.[22] In a population-based register study in Sweden disorders of calcium metabolism including vitamin D deficiency were associated with increased odds of long bone fractures and of rib fractures.[23] A Polish study of children with

fractures found significantly lower 25OHD levels in children with low energy fractures than in a control group.[24] Similar findings were noted in studies from the USA, Saudi Arabia and Egypt.[25-27]

2.2 Alternative views

The recognition of vitamin D deficiency as a significant cause of unexplained fractures has not been unchallenged. In 2011 Schilling et al[28] published a study of 118 children with fractures in whom eight had deficient levels of 25OHD. They found no relationship between 25OHD levels and the diagnosis of accidental injury versus non-accidental injury. The authors' criteria for a diagnosis of abuse could mean that cases in which fractures were actually caused by vitamin D deficiency would be included in that group. There were other difficulties with this paper, summarised in an invited commentary.[29]

In 2012 Perez-Rossello et al[30] reported a study of radiographic findings at the wrists and knees in children aged between 8 and 24 months with serum 25OHD levels lower than 20 ng/ml. Only two children had radiographic evidence of rickets and none had fractures. They concluded that fracture risk was low in vitamin D deficiency. One difficulty with this interpretation is that most infants who have fractures thought to be due to vitamin D deficiency are younger than 8 months. In addition there is evidence that even in severe vitamin D deficiency there may be none of the conventional radiological signs of rickets in young infants (see section 2.4). The subsequent correspondence[31,32] should be noted.

In 2019 Servaes et al[33] reported a study of radiological signs of rickets in 79 infants with fractures with a median age of 4 months. None of the children had conventional radiological evidence of rickets. Only six of the children had 25OHD levels lower than 20 ng/ml. The authors concluded that radiological evidence of rickets was uncommon in their group of infants with fractures. However there was no information on maternal vitamin D status and little exploration of the wider differential diagnosis. They did not address the concern that in infancy severe deficiency may not be accompanied by radiological abnormalities (see section 2.4).

2.3 Clinical biochemistry

Serum 25OHD is regarded as the most appropriate measure of vitamin D status. The most widely used level below which significant deficiency is conventionally diagnosed is 20 ng/ml (50 nmol/L). Consensus on this issue is not complete; some authors have made a case for a higher level.[34] It should be noted that the various assays available may give somewhat different values for the same sample.[35-37]

Other relevant biochemical investigations include serum calcium, inorganic phosphate, alkaline phosphatase and parathyroid hormone (PTH). All have limitations. For example in a study by Haarburger et al[38] in South Africa vitamin D deficiency was defined as below 18 ng/ml; normal values for serum calcium and PTH were frequently found. Similarly Atapattu et al[39] defined deficiency as below 15 ng/ml and found that, while there were significant relationships between 25OHD levels and both calcium and PTH, most of the deficient children had values for calcium and PTH within the reference ranges.

Since the liability to fracture depends on the vitamin D status at the time the bones were forming in intrauterine life the 25OHD figures in the months after birth may be unhelpful. The assay is useless if the child has been treated with vitamin D. In any event serum 25OHD levels in infants rise rapidly after birth, particularly if formula-fed.[40] There are two ways of gaining an insight into the likely status at birth. One is to check the mother's level provided that there has been no great change in her diet or lifestyle since the birth. Little change ordinarily takes place in the vitamin D status of mothers postpartum.[41] A second approach is to determine the 25OHD level in dried blood spots from neonatal screening. As with serum assays it is important to specify the analytical method used.[42-43]

2.4 Radiology and histology

The classical radiological features of vitamin D deficiency rickets, particularly at the wrists and knees, have been recognised for many years. However it is important to note that severe vitamin D deficiency may occur without any of the conventional radiological abnormalities. This may be found in cases with fractures[1,44] and with hypocalcaemic seizures.[45,46] In a large study in China of fetal and neonatal autopsies[47] 44 infants had histological evidence of rickets: 33 had radiological abnormalities in the ribs, 17 had abnormalities in the ulna and only nine had abnormalities in the radius. In a study in the United Kingdom of 41 cases of sudden infant death 13 infants had serum 25OHD levels of less than 20 ng/ml. Of these, nine had some histological abnormalities in the ribs but only four had any radiological features to suggest rickets.[48] In a similar study of autopsies in children[49] 43 children had 25OHD levels below 20 ng/ml; of these, 18 had histological abnormalities of the growth plate in the ribs. Only four had radiological abnormalities including one (premature) child with multiple fractures.

An additional problem should be noted. In 1946 Caffey[50] noted fractures at the ends of long bones in infants with subdural haematoma and suggested that trauma was the cause since no evidence of metabolic disorder was found. In 1953 Silverman[51] reported three infants with metaphyseal fractures, some with a history of pulling and/or twisting forces. Since that time it has been assumed that all such fractures or fracture-like appearances reflect non-accidental injury. In one review[52] metaphyseal corner fractures were described as 'virtually pathognomonic and highly specific features of child abuse'. Since then a series of papers from Kleinman and his colleagues[53,54] have reinforced this opinion. Later doubts arose as to whether these frequently seen anomalies were fractures at all and they were renamed 'classical metaphyseal lesions' (CML) but still confidently ascribed to abuse.

The difficulty with this view is that metaphyseal lesions have long been described in various metabolic disorders in the first year of life. These include hyperparathyroidism,[55] copper deficiency,[56] Menkes' syndrome,[57] vitamin C deficiency[58] and neuromuscular disease associated with hypokinesia in utero.[59] More recently it has been demonstrated that 'bucket-handle' and 'corner fracture' CMLs are strikingly similar to the appearances of healing rickets. Other features of CMLs also argue against a traumatic cause and in favour of a metabolic cause.[60] CMLs have also been described in circumstances where abuse could be excluded with confidence: after an 'easy' delivery by caesarean section,[61] with normal

handling in a neonatal intensive care unit[62] and with physical therapy.[63]

In contrast, Perez-Rossello et al[64] argue against metabolic causation of CMLs. They found no histological or radiological evidence of rickets in nine infants with CMLs who died as a result of intracranial problems allegedly caused by homicide. No laboratory findings were available and there was no attempt to exclude causes of CMLs other than rickets. In another response Oestreich[65] described differences between 'CMLs of abuse' and rachitic changes but conceded that the appearances of the former were only 'somewhat different' from those of healing rickets. Again the wider differential diagnosis of CMLs was not addressed.

Other authors have drawn attention to the various artifacts that may be mistaken for CMLs.[66] In a recent review Miller and Mirkin[67] also contended that many CMLs were artifacts or else reflected metabolic bone disorders. Their most compelling argument against a traumatic cause of CMLs is the histological finding of a lack of hemorrhage.

3. Vitamin C deficiency

Scurvy has been recognised as a distinctive disorder since at least the 16th century. In the 18th century James Lind, a surgeon's mate in the Royal Navy (and later a physician) demonstrated that its cause was the lack of fresh vegetables and that citrus fruits were effective in treatment. In the 1930s it was demonstrated that the active component of fruit and vegetables was ascorbic acid, which was then called vitamin C. It was also shown that many animals could synthesise ascorbic acid but not humans, primates or guinea pigs.[68]

Since then many of the biochemical roles of ascorbic acid have been identified. In particular it is an essential co-factor in the hydroxylation of lysine to hydroxylysine and of proline to hydroxyproline. Thus ascorbic acid is essential for the formation of collagen.[69] Defects in collagen synthesis underlie many of the clinical features of vitamin C deficiency. In adults these include tender and bleeding gums, spontaneous bruising and pain in bones (mainly as a result of sub-periosteal bleeds). In children the most common symptoms are pain in limbs and often limited movement, sometimes leading to an apparent paralysis (or 'pseudoparesis'). The best-known early summary of the clinical features of scurvy was by Thomas Barlow in 1883 and the condition was long known as Barlow's disease (Evans 1983). As early as 1894 intracranial bleeding was reported in children with scurvy.[70,71]

3.1 Vitamin C deficiency and fractures

Spontaneous fractures in children with scurvy were recognised in Barlow's original paper. He mentioned fractures near the epiphyses. Transverse fractures of two long bones were described by Sutherland in 1894. Metaphyseal fractures are well recognised.[72] Both diaphyseal and metaphyseal fractures occur spontaneously in Rhesus monkeys with vitamin C deficiency.[73]

There are a few reported cases in which vitamin C deficiency bone disease has been initially misdiagnosed as non-accidental injury[74,75] and one in which a child had both rickets and scurvy.[76] In one case, only identified in retrospect, a child was found at nine weeks of age to have metaphyseal lesions, a probable old rib fracture and periosteal reactions on one tibia.[77] These were reported as having a 'high

specificity for non-accidental injury'. Despite reports from birth that the child had been seen regularly with no evidence of trauma, he was removed from the parents. It later became known that his mother had from the fifth month of pregnancy severe nausea, a very limited diet and, by the time of birth, multiple bruises and swollen bleeding gums. On being treated with ascorbic acid all these problems resolved. The relevance of the mother's severe scurvy to her son's spontaneous fractures and fracture-like abnormalities was not recognised.

Although overt scurvy is rare, it is known that vitamin C deficiency is not uncommon even in Western countries.[78] There is a clear distinction to be made between 'rarely diagnosed' and 'rarely considered'.

3.2 Clinical biochemistry

The investigation of an individual for vitamin C status requires considerable attention to detail, not least because of the instability of ascorbic acid. Assays for plasma ascorbic acid are widely used in surveys. One protocol is that blood samples are placed immediately on ice, delivered to the laboratory within one hour, separated in a refrigerated centrifuge and metaphosphoric acid added to the plasma.[79] Even then, while low values may reflect deficiency, they may also occur in inflammatory disease. One way round this problem is to use assays of leucocyte ascorbic acid. An alternative involves assessment of stores with a loading dose of ascorbic acid followed by estimation of urinary excretion.

4. Differential diagnosis

Vitamin D deficiency and vitamin C deficiency are but two of the disorders to be considered in the child with unexplained fractures in the first year of life.[80] The best known is osteogenesis imperfecta (OI), a large group of genetic disorders most commonly caused by defects in collagen. Genetic factors contributing to fracture risk in infancy include disorders other than OI, some characterised by joint laxity in patients and relatives.[81,82] Spontaneous fractures have long been recognised after preterm birth;[83-86] while identified correctly when the child is still in hospital, these may be misdiagnosed as abuse after the child has gone home. Copper deficiency and Menkes' syndrome also cause multiple fractures including CMLs.[57,87] Copper, like ascorbic acid, is an essential co-factor in the synthesis of collagen.

There are still other cases that are unexplained but unlikely to reflect abuse. We investigated a large group of such patients and called the diagnosis 'temporary brittle bone disease' because we could not identify the cause. An alternative name is 'metabolic bone disease of infancy'.[67] Such patients had many clinical features in common, particularly the often gross discrepancy between the fractures and any superficial evidence of injury.[88] We also reported patients in whom inflicted injury could be excluded with confidence because the fractures took place in hospital.[89] When 61 such patients were returned to their parents, none had subsequent evidence of abuse.[90]

5. Conclusions

Unexplained fractures and asymptomatic fracture-like anomalies in infants have a wide differential diagnosis including deficiencies of vitamin D and vitamin C in the mothers during pregnancy. Much further research is needed to improve the recognition of all these disorders.

Such research calls for open minds and an insight into the various underlying causes, not least because a mistaken diagnosis of abuse is severely damaging to a family and particularly to the child concerned.

Authorship

CRP conceived this study and wrote the initial manuscript. ECP reviewed and edited the text.

Acknowledgements

We are greatly indebted to Mrs Sally Paterson for her help in preparing this review.

Conflicts of interest

None

Note

Since this review went to press an important paper has been published by Miller, Stolfi and Ayoub in the US .[91] This is a series of 75 infants with metabolic bone disease of infancy whose clinical features are very similar to those previously described in separate series as temporary brittle bone disease. This paper also explores the likely causes of this syndrome including maternal vitamin D deficiency.

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