A case series of vitamin D deficiency in mothers affecting their infants

Vitamin D plays an essential role in calcium homeostasis, prevention of rickets and the development and maintenance of the skeleton. We present three cases representing the spectrum of maternal vitamin D deficiency affecting the infants of deficient mothers. We would like to highlight the importance of antenatal screening of vitamin D in high-risk populations and the treatment of infants and mothers at risk following detection of deficiency.

Atisha Pandya
Third Year Medical Student, Guy's, King's and St Thomas' School of Medicine

Ahmed Aldouri[1]
MBBS, ST1 Paediatrics

Nikila Pandya[1]
MD, DCH, FRCPCH, Consultant Paediatrician
nikilapandya@nhs.net

Bim Bhaduri[1]
FRCPCH, Consultant Paediatrician

[1]Department of Paediatrics, Maidstone Hospital

Keywords

rickets; vitamin D deficiency; tetany; growth failure; short stature; long QT; ECG

Key points

Atisha P., Ahmed A., Nikila P., Bim B. A case series of vitamin D deficiency in mothers affecting their infants. *Infant* 2010; 6(6): 196-201.

1. Vitamin D deficiency is common in the immigrant population. Dress code can be a contributory factor.
2. Antenatal screening for this high risk group is important.
3. It is vital maternal vitamin D levels are normal if the mother is breast feeding.
4. Vitamin D deficiency should be considered in short stature and unexplained hypocalcaemia.

Vitamin D deficiency continues to be a public health problem in many countries despite the presence of cheap and effective means of preventing the disease. The deficiency is associated with rickets in growing children and osteomalacia in adults. Infants, toddlers and adolescents in 'at risk' ethnic minorities (eg Asian, African Caribbean and Middle Eastern) are particularly likely to be vitamin D-deficient or to have rickets. Other clinical manifestations during childhood include hypocalcaemic seizures, fractures, lower-limb deformities, abnormal dentition and delayed developmental milestones. Rickets remains a problem in the UK, especially in certain ethnic minority groups. Growth rate is likely to be an important factor in determining the mode of presentation. Unexplained hypocalcaemia should be attributed to vitamin D deficiency in at risk ethnic minority groups until proven otherwise. The deficiency is attributed to insufficient intake, religious practices and reduced exposure to sunlight, latitude and altitude. Paediatricians and other healthcare professionals should try to ensure that children and adolescents receive daily vitamin D requirements appropriate for their risk factors, traditions, and customs. Antenatal screening of the high-risk immigrant population is warranted. Additionally, it is important to use every opportunity to ensure that effective preventive strategies are put in practice. It is recommended that healthy infants, children and adolescents take at least 400 IU vitamin D per day to prevent rickets and vitamin D deficiency[1-4].

Case 1

A six-month-old thriving Afghani baby weighing 8.8kg presented to accident and emergency with a history of floppy episodes and twitching of face and all four limbs lasting for five minutes at a time

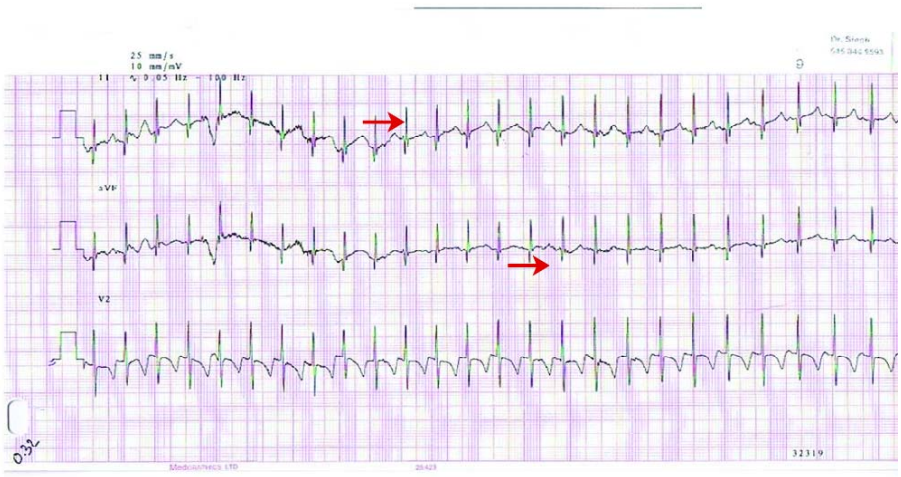

FIGURE 1 ECG showing prolonged QTc in Case 1.

1a

BABY		
Biochemistry	**Level at presentation (normal range)**	**Three months later on treatment**
Serum Ca	1.64mmol/L (2.2-2.74)	2.27mmol/L
Ionised serum Ca	1.48mmol/L	2.24mmol/L
Serum phosphate	1.09mmol/L (0.81-2.26)	2.14mmol/L
Alkaline phosphatase	808IU/L (1-462)	166 U/L
Magnesium	0.82	0.86
Vitamin D	10nmol/L ** (75-200)	

1b

MOTHER	At presentation
Serum Ca	2.12mmol/L*
Adjusted Ca	1.98 mmol/L*
Vitamin D	Unavailable

TABLES 1a and b Biochemical results for the mother and baby in Case 1 (*low, **very low)

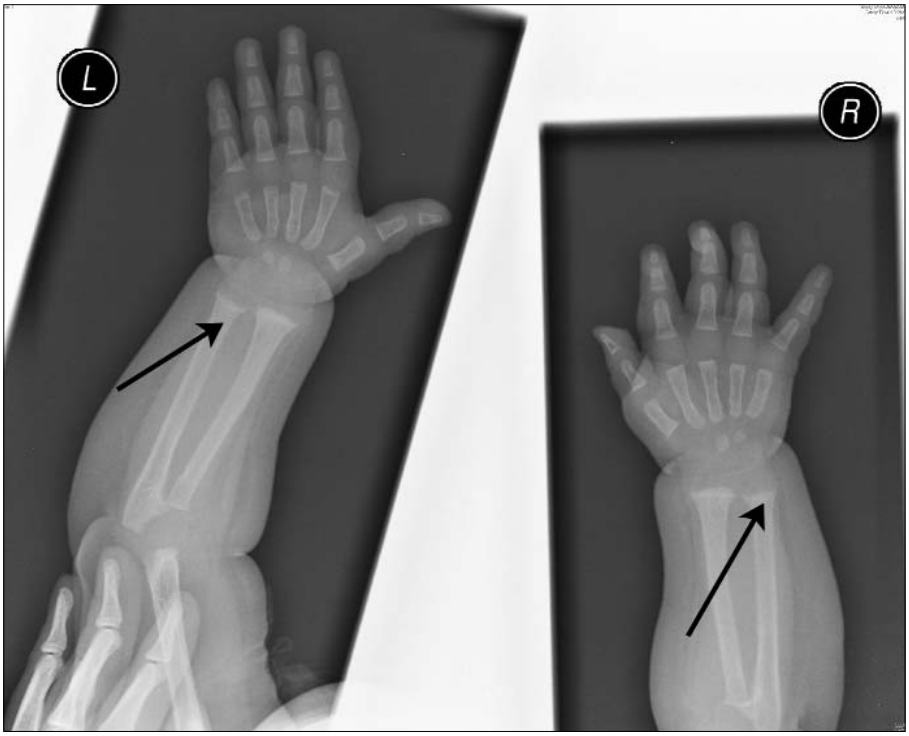

FIGURE 2 Widening, cupping and fraying of epiphysis – Case 1 at presentation.

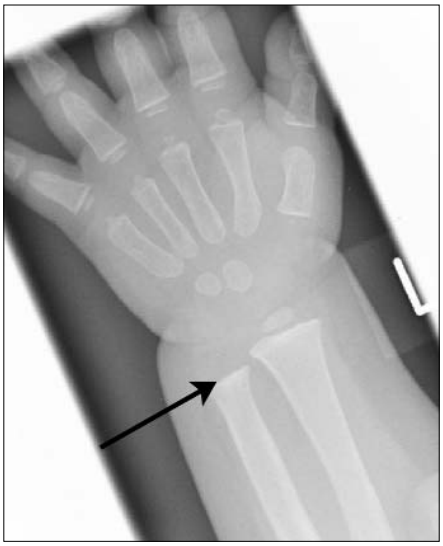

FIGURE 3 Case 1 – X-ray shows marked improvement with healed rickets three months post treatment.

with full recovery. In the intervening time she was very well. The young mother was following a veiled dress code and was exclusively breast feeding.

The latest episode was associated with a floppy head, rolling of eyes, frothing, jerking of all four limbs, blue lips and face. On arrival the baby's blood sugar was 7.4 mmol/L, temperature 37°C. Her birth history was normal. Examination and development were normal. Blood investigations were carried out. A metabolic screen, including serum amino acids and lactate, was normal. An ECG was performed revealing a prolonged QTc of 0.57 (normal 0.35-0.45) (**FIGURE 1**).

A cardiology referral was made. The reason for the prolonged QTc was the baby's hypocalcaemia (**TABLE 1**). She continued to have several seizures a day each lasting up to six minutes with complete neurological recovery. She was started on sodium valproate which was subsequently discontinued.

An X-ray of the baby's wrists showed frank rickets (**FIGURE 2**).

Both the mother and baby were treated with Alfacalcidol 600 nanograms daily and calcium supplements for six months. The baby showed a marked improvement at three months (**FIGURE 3**). The mother is continuing to take vitamin D supplements.

Case 2

A two-year-old black child was referred for delayed motor milestones. This young child was "talking not walking" according to the referral letter from the GP. She was still breast fed and mother was finding weaning difficult.

On examination, she had marked hypotonia, with evidence of severe rickets and widening of wrists and rachitic rosary (**FIGURES 4 and 5**).

Her height and weight were on the 9th centile at presentation and her biochemistry revealed severe vitamin D deficiency (**TABLE 2a**). She made a good recovery following treatment with a combination of Ergocalciferol 3000 units

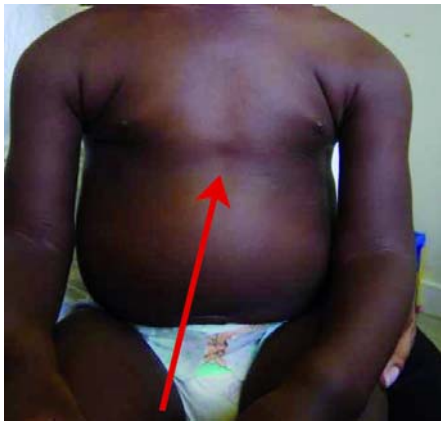

FIGURE 4 Showing Harrison's sulcus, bell shaped chest and widening at the wrists.

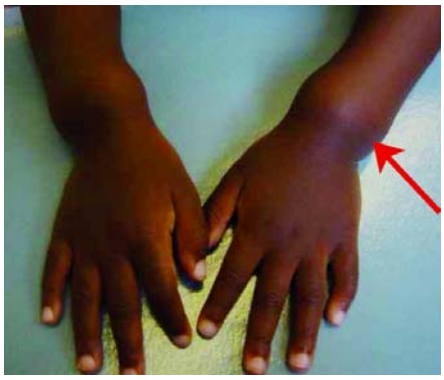

FIGURE 5 Widened wrists.

BABY 2a

Date	Level at presentation (normal range)	On treatment	Six months later
Serum Ca	1.6mmol/L (2.3-2.75)	2.4	2.3
Alkaline phosphatase	1679† IU/L (145-380)	359	433
Magnesium	0.88mmol/L (0.6-1.16)		
Vitamin D	19**nmol/L (>75)		
Phosphate	1.2mmol/L (1.5-2.2)	1.64	1.66

MOTHER	At presentation 2b
Serum Ca	2.3mmol/L
Phosphate	1.2mmol/L
Vitamin D	29**nmol/L (>75)

TABLES 2a and b Biochemical results for the mother and baby in Case 2 (†very high, **very low).

daily and calcium and phosphate supplements for six months (**FIGURE 7**).

She was walking without support six weeks into her treatment. The growth chart (**FIGURE 8**) shows that following treatment with vitamin D and Ca her weight increased to the 75th centile and height to the 50th centile one year later. She is now eight and half years old and is thriving having reached the 98th centile for height after presenting at the 9th centile. Early treatment has allowed her to achieve her full growth potential.

The child's mother was also found to have very low vitamin D levels at presentation (**TABLE 2b**) and was treated with vitamin D and calcium supplements.

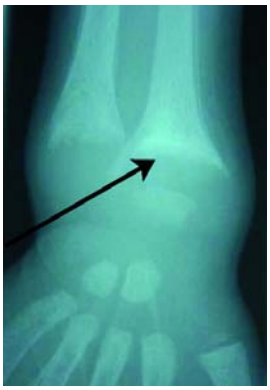

FIGURE 6 Showing widening, cupping and fraying epiphyses pathognomonic of rickets.

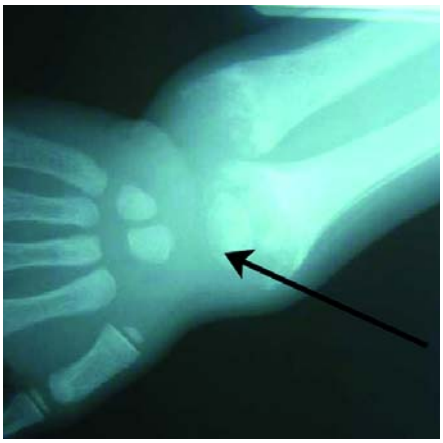

FIGURE 7 Healing rickets.

Case 3

A two-year-old child was referred for short stature, having dropped two centiles from her length at six months. She was breast fed till six months of age before weaning appropriately. Her development was appropriate. She was 84cm on the 9th centile having previously been on the 75th centile. There was no clinical evidence of rickets. Mother was noted to have vitamin D deficiency during her pregnancy in 2007 and was treated partially and then unfortunately lost to follow-up. She was retested in 2010 due to tingling of the face and symptoms suggestive of hypocalcaemia. The infant was tested in view of her symptoms and the maternal history and found to be severely deficient like her mother (**TABLE 3**). Treatment was instituted with 600IU of cholecalciferol daily for six months.

This case highlights the importance of checking vitamin D levels along with bone chemistry for unexplained short stature

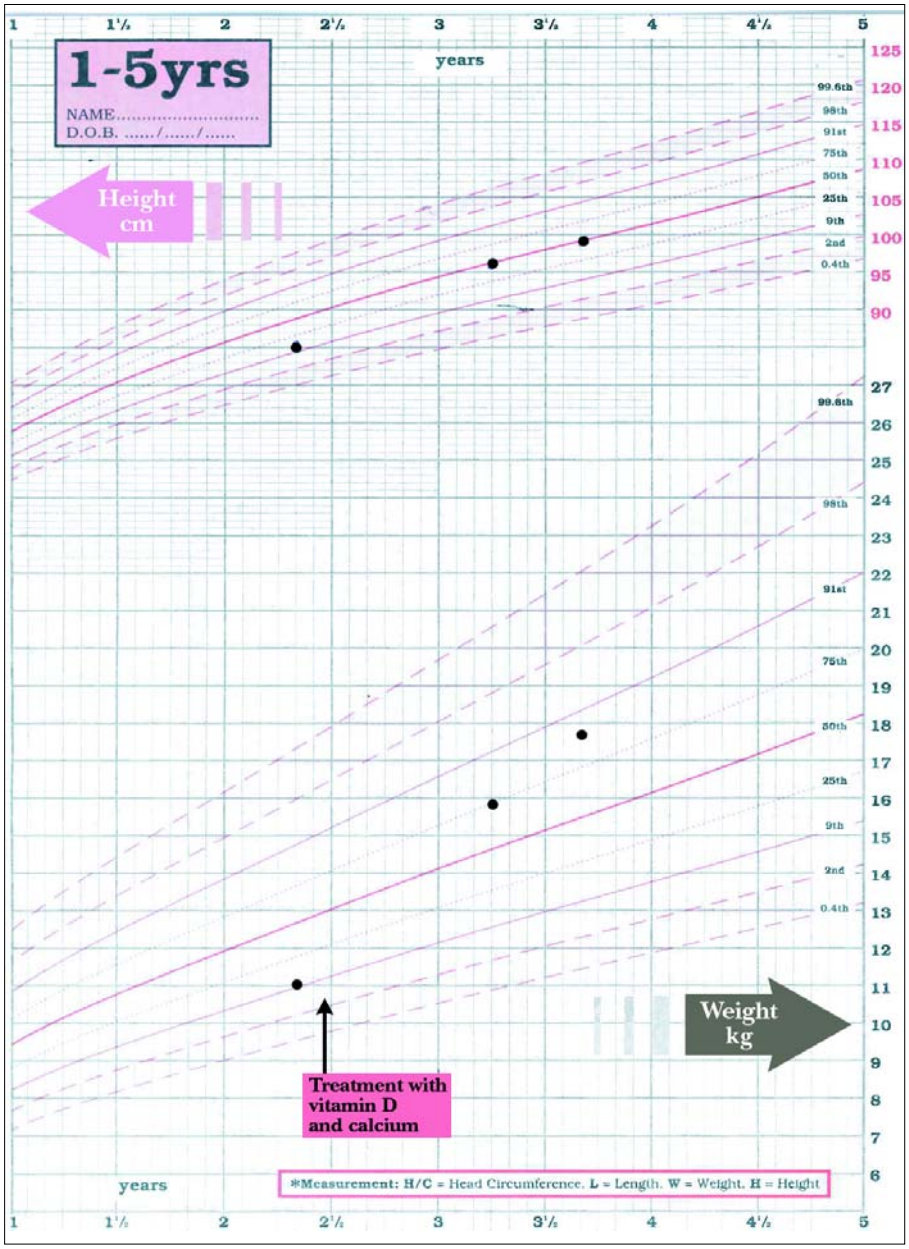

FIGURE 8 Growth chart showing increase in height and weight on treatment – Case 2.

INFANT 3a

Date	Level at presentation (normal range)	Five months later, on treatment with vitamin D and Ca
Adjusted calcium	2.22mmol/L (2.24-2.74)	2.27
Vitamin D	15.3nmol/L** (>75)	29.7
Alkaline phosphatase		172

MOTHER 3b

Date	In 2007	In 2010 restarted on treatment at double dose	On treatment five months later
Adjusted Ca	1.98	1.97	
Vitamin D	49*	15.6	24.7
Serum phosphate		1.11	

TABLES 3a and b Biochemical results for the mother and baby in Case 3 (*low, **very low).

and rechecking during treatment to ensure appropriate levels are achieved.

Discussion

Historical background

The first detailed report of a condition caused by a deficiency of vitamin D was that of rickets, as seen in the 17th century by Professor Francis Glisson and Dr Daniel Whistler. In 1906 Hopkins first postulated the existence of essential dietary factors necessary for the prevention of diseases such as scurvy or rickets[5]. It wasn't until the period between 1910 and 1930 that a major breakthrough occurred in the understanding people had of the cause of rickets and their new knowledge of vitamins.

In 1921 an experiment was devised to establish the cause of rickets in dogs by Sir Edward Mellanby, upon which he concluded that the lack of a certain fat soluble vitamin was the cause[6].

Following a series of other experiments that determined the light sensitive properties of the vitamin, the discovery of an antirachitic factor occurred and this was classified as vitamin D. The chemical structures of the forms D_2 and D_3 we know today were determined in 1932 and 1936 at the University of Gottingen, Germany[7].

Main function of vitamin D

It is largely through an historical accident that vitamin D was classified in the early 1920s as a vitamin rather than as a steroid hormone. A more accurate description would be to classify it as vitamin D prohormone, produced photochemically in the skin from 7-dehydrocholesterol.The molecular structure of vitamin D is closely allied to that of classical steroid hormones (eg oestradiol, cortisol, and aldosterone) because they all have the same root cyclopentanoperhydrophenanthrene ring structure[8]. The maintenance of basic physiological calcium homeostasis within the body is a main feature of vitamin D. It is a fat soluble vitamin whose two major forms are D_2 (ergocalciferol) and D_3 (cholecalciferol), the latter being produced in the skin of vertebrates as a result of exposure to sunlight. This conversion of provitamin D_3 to vitamin D_3 occurs when UV light hits the skin, causing a reaction to occur. Both ergocalciferol and cholecalciferol are metabolised by the liver to make the major circulating forms of the vitamin 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 which are detected by most tests[9]. After the first hydroxylation, the kidneys play a vital role in turning the circulating forms of the vitamin into 1,25-dihydroxyvitamin D_2 and 1,25-dihydroxyvitamin D_3. The final hydroxylation within the kidneys gives rise to the active forms of vitamin D which then go on to help increase absorption of calcium and phosphate from the small intestine, aid in the mineralisation of the bone matrix as well as inhibiting the synthesis of parathyroid hormone[10].

Epidemiology

The main populations at risk of vitamin D deficiency are African Americans and those from the Asian subcontinent[11]. The at risk groups have a higher concentration of melanin in their skin which acts as a natural barrier to UV light and therefore limits the synthesis of vitamin D. Hypovitaminosis D is also common in the elderly, with up to 50% of the older population being affected. During the year there are only a few months in which the skin is able to synthesise vitamin D due to the differing wavelengths of sunlight. In countries with a high latitude around the world, the range of light needed is only available for limited periods of time during the day[12].

Aetiology and associated conditions

Since it plays such a vital role in calcium homeostasis, a deficiency of vitamin D can be quite severe. Maternal vitamin D is of great importance when analysing the unborn child's vitamin D levels which if low can lead to a number of different conditions. Vitamin D deficiency can be a result of a poor diet, lack of appropriate sunlight exposure, hereditary conditions which affect the liver and kidney along with certain disorders which somehow decrease the amount of vitamin D the skin can absorb. Very few foods have adequate vitamin D content and even those foods which are enriched with vitamin D are not very effective. The result of the deficiency can cause poor bone mineralisation which then causes diseases such as rickets in infants and osteomalacia in adults. It has been associated with a higher risk of a number of autoimmune disorders, cancer and infectious diseases[13]. It is also thought that darker pigmented skin doesn't absorb sunlight and synthesise vitamin D as well as lighter skin due to melanin acting as a natural sun block or barrier. The wavelength of UV light is optimum for vitamin D absorption during the summer months and generally during winter very little vitamin D is synthesised due to a change in wavelength.

In children vitamin D deficiency can cause a number of complications including tetany, rickets and short stature. Neonatal tetany is often a complication of low vitamin D levels in the mother during pregnancy. This in turn affects the newborn child who due to an inadequate intake during gestation develops hypocalcaemia. Tetany can be caused by a parathyroid hormone deficiency, hyper or hypo magnesaemia or a vitamin D deficiency. Even if a baby is breastfed they can still be deficient in vitamin D as the amount of this vitamin excreted in breast milk is limited and corresponds directly with the maternal serum levels of vitamin D[14]. Quite often breastfeeding mothers with hypovitaminosis D are recommended to take supplements to help maintain an acceptable vitamin D level.

The tetany that occurs in neonates due to hypocalcaemia is a result of the low levels of calcium causing neurons to over excite as their threshold for excitation decreases. This results in longer, repetitive more prolonged depolarisation which gives rise to tetany. The over excitability of the muscles is not the cause of tetany as the hypocalcaemia depresses the release of neurotransmitter acetylcholine at neuromuscular junctions, but the neuronal depolarisation overcomes the inhibition of muscle contraction leading to jerky movements.

A prolonged QTc interval, as witnessed in our first case, is another recognised manifestation of hypocalcaemia. The QT segment on ECG reflects both the period of depolarisation (influx of Na^+, Ca^{2+}, efflux of K^+) and repolarisation (extraction of Na^+, Ca^{2+}) of cardiac myocytes. Lengthening QTc is associated with a higher risk of Torsades de pointes, ventricular tachycardia (VT) and ventricular fibrillation (VF)[15,16].

The prolongation of the QTc is due to lengthening of the ST segment, which is directly proportional to the degree of hypocalcaemia or, as otherwise stated, inversely proportional to the serum calcium level. It is also commonly accepted that hypocalcaemia with its accompanying increase in the QTc interval does not affect the QRS complex, and therefore does not produce an intraventricular conduction defect, and generally does not cause T-wave changes as it does not affect phase 3 of the action potential[16].

Rickets is a condition characterised by a softening of the bones, often leading to a bow-like appearance of the legs in children. In recent times, there has been a rise in children from ethnic minorities suffering from rickets due to poor diet and a subsequent vitamin D and calcium deficiency. Other groups highly at risk are those children who were born prematurely and those who are on medications that affect vitamin D synthesis and absorption. African American infants who are exclusively breastfed have also been seen to be at risk as maternal milk does not provide all the vitamin D needed[17]. Fatty oily fish seems to be one of the only natural nutritional sources of vitamin D available. In some countries like the United States of America, milk has vitamin D added to help prevent deficiency.

The incidence of rickets is higher in sunny areas like the Middle East, as often the children are swaddled in clothes which decrease their sunlight exposure. In certain African countries, rickets can be caused due to a high corn diet which does not provide a lot of calcium or vitamin D[18].

Symptoms of rickets include pain, bowing of legs, short stature, fragile bones which are more susceptible to fractures and breaks and dental problems.

The most common method to diagnose rickets is via a combination of blood tests and X-rays. The blood test of a child with rickets often shows a high level of serum alkaline phosphatase along with low calcium, and phosphorus levels. Metabolic acidosis is also common. The X-rays are characterised by loss of calcium of bones and different changes in the shape and structure of the bones. If all the tests still remain inconclusive, a bone biopsy can be performed[19].

Another condition associated with low intake of vitamin D is short stature, defined as being two or more standard deviations below the average/mean height for their appropriate age, sex and race. This can also be defined as being below the third percentile in height. Short stature can occur due to rickets as the bones are soft and therefore do not grow and ossify as normal. In cases of idiopathic short stature the impact of vitamin D is profound.

Studies have shown that the region which is connected to adult height contains a receptor known as the vitamin D receptor (VDR) gene. This suggests that vitamin D has a very important role to play in short stature and normal growth. Nutritional deficiencies are a contributing cause to short stature although often poor weight gain is easier to spot and more noticeable than short stature[20].

Although the index diseases for vitamin D deficiency have long been considered to be rickets (for children) and osteomalacia (for adults), there has been a growing conviction that less severe degrees of deficiency may also produce skeletal disease[21]. In 1990 Parfitt introduced an important reconceptualisation of the bone disease attributable to vitamin D deficiency, for which he coined the term hypovitaminosis D osteopathy. He identified three stages of disease, related to increasing degrees of vitamin D depletion, with stage 1 being the mildest form of deficiency (reduced intestinal absorption of calcium, with consequent diminution of skeletal calcium reserves and accompanying osteoporosis but no evidence of osteomalacia) and stage 3 most severe (hypo absorption of calcium and osteomalacia/rickets evident clinically, biochemically, and histologically)[22]. This reconceptualisation was important in recognising that disease can occur in mild deficiency, in the form of osteoporosis, as well as in severe vitamin D deficiency.

Management and treatment of vitamin D deficiency

As with most medical conditions, preventative measures are more affective than actual treatment. Pregnant and breastfeeding mothers should be advised to take a high calcium high vitamin D diet to ensure the nutrients are passed down to the baby. A high phosphorus diet is also advised as are vitamin D supplements, suitable time in the sun, and if needed cod liver oil supplements. Along with a healthy diet, certain conditions existing due to vitamin D deficiency, eg rickets often need licensed medication.

Specifically, breastfeeding children up to the age of 24 months are recommended to take 400 IU of vitamin D_3. Of those, children with darker skin should take between 400-1000 IU vitamin D_3 up to 18 years of age, to ensure a deficiency does not occur.

Lactating, ageing, or pregnant adults are recommended to take between 800-1000 IU a day or 50,000 IU a month.

Patients suffering from malabsorption syndromes should have 50,000 IU vitamin D_2 a week. Darker skinned individuals are often recommended to increase their vitamin D intake, especially those living in areas of higher latitude[23].

Conclusion

The above three cases demonstrate the importance of early recognition and treatment of vitamin D deficient mothers and their children, particularly those who are exclusively breastfed as infants. These cases also highlight the importance of antenatal screening and prophylactic vitamin D supplementation for mothers at high risk of vitamin D deficiency. The complications of deficiency vary according to the severity of the deficiency and can be both chronic in presenting as short stature or rickets, or present acutely as tetany and seizures, and can even be life threatening – prolonged QT interval resulting in

ventricular arrhythmias and sudden death. Clinicians in the primary care setting or as paediatricians therefore need to carry a low threshold of suspicion in all children with an unexplained hypocalcaemia born to mothers at high risk of vitamin D deficiency, and to ensure that effective preventive strategies are put into practice where possible.

References

1. **Holick M.F.** Vitamin D deficiency: what a pain it is. *Mayo Clin Proc* 2003; **78**(12): 1457-59.
2. **Callaghan A.L. et al.** Incidence of symptomatic vitamin D deficiency. *Arch Dis Child* 2006; **91**(7): 606-07. Epub 2006 Apr 4.
3. **Ladhani et al.** Presentation of vitamin D deficiency. *Arch Dis Child* 2004; **89**(8): 781-84.
4. **Unuvar T., Buyukgebiz A.** Nutritional rickets and vitamin D deficiency in infants, children and adolescents. *Pediatric Endocrinol Rev* 2010; **7**(3): 283-91.
5. **Hopkins, F.G.** The analyst and the medical man. *Analyst* 1096;31:385-404.
6. **Wolf G.** The discovery of vitamin D: The contribution of Adolf Windaus – The American Society for Nutritional Sciences. *J Nutr* 2004; **134**: 1299-302.
7. **Crowfoot-Hodgkin D., Webster M.S., Dunitz J.D.** Structure of calciferol. *Chem Industry* 1957; 1148-49.
8. **Norman A.W.** Sunlight, season, skin pigmentation, vitamin D and 25-hydroxyvitamin D: Integral components of the vitamin D endocrine system. *Am J Clin Nutr* 1998; **67**: 1108-10.
9. **DeLuca H.F.** Vitamin D metabolism and function. *Arch Intern Med* 1978; 138(Suppl 5): 836-47.
10. **Joshi D. et al.** Vitamin D deficiency in adults. *Aust Prescr* 2010; **33**: 103-06.
11. **Harris S.S.** Symposium: Optimizing Vitamin D Intake for Populations with Special Needs: Barriers to Effective Food Fortification and Supplementation Vitamin D and African Americans- American Society for Nutrition. *J Nutr 2006;* **136**: 1126-29.
12. **Gloth F.M. et al.** Vitamin D deficiency in home-bound elderly persons. *JAMA* 1995; **274**: 1683-86.
13. **Holick M.F. et al.** Vitamin D deficiency: A worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87**(4): 1080S-6S.
14. **Dawodu A., Wagner C.L. et al.** Mother-child vitamin D deficiency: An international perspective. *Arch Dis Child* 2007; **92**(9): 750-53.
15. **Mangat J.S., Till J., Bridges N.** Hypocalcaemia mimicking long QT syndrome: Case report. *Eur J Pediatr* 2008; **167**(2): 233-35.
16. **RuDusky B.M.** ECG abnormalities associated with hypocalcemia. *Chest* 2001; **119**(2): 668-69.
17. **Kreiter S.R., Schwartz R.P., Kirkman H.N. Jr et al.** Nutritional rickets in African American breast-fed infants. *J Paediatr* 2000; **137**(2): 153-57.
18. **Gartner L.M., Greer F.R. et al.** Prevention of rickets and vitamin D deficiency: New guidelines for vitamin D intake. American Academy of Paediatrics. *Pediatrics* 2003; **111**(4): 908-10.
19. **Greer F.R., Finberg L.** Rickets. E Medicine. http://emedicine.medscape.com/article/985510-overview. April 2010.
20. **Dempfle A. et al.** Evidence for involvement of the vitamin D receptor gene in idiopathic short stature via a genome-wide linkage study and subsequent association studies. *Hum Mol Genet* 2006; **15**(18): 2772-83.
21. **Heaney R.P.** Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr* 2004; **80**(suppl):1706S-9S.
22. **Parfitt A.M.** Osteomalacia and related disorders. In: Avioli LV, Krane SM, eds. Metabolic bone disease and clinically related disorders. 2nd ed. Philadelphia: WB Saunders. 1990: 329-96.
23. **Holick M.F.** Vitamin D deficiency. *N Engl J Med* 2007; **357**(3): 266-81.