Presentation of vitamin D deficiency

S Ladhani, L Srinivasan, C Buchanan, J Allgrove

Aims: To describe the various ways in which vitamin D deficiency presents in children in selected districts of London and to identify which factors, if any, determine the mode of presentation.

Methods: Retrospective review of patients presenting to Newham General, Royal London, Great Ormond Street, and King’s College Hospitals between 1996 and 2001 with either hypocalcaemia or rickets caused by vitamin D deficiency. Children with plasma 25-hydroxyvitamin D levels <25 nmol/l (10 ng/ml) were considered to have vitamin D deficiency.

Results: Sixty five children, mostly from Black or Asian ethnic minority groups, were identified, 29 of whom had hypocalcaemic symptoms. Seventeen of these had no radiological evidence of rickets. The remainder (48 children) had radiological evidence of rickets with or without clinical signs. Symptoms and signs reverted to normal in all cases with vitamin D supplementation. All children who presented with symptomatic hypocalcaemia were aged either <3 or >10 years. There was a strong correlation between age at presentation and population growth velocity reference data.

Conclusions: Rickets remains a problem in the UK especially in “at risk” ethnic minority groups. Symptomatic hypocalcaemia is an important, but under-recognised presenting feature. 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 proved otherwise.

METHODS

The case records of children aged 0–16 years at the time of diagnosis with vitamin D deficiency treated at three north-east London hospitals—Newham General Hospital, Royal London, and Great Ormond Street—or King’s College Hospital, in southeast London, between 1996 and 2001 were studied retrospectively. A predefined questionnaire was used to extract relevant information from the case notes. Calcium, phosphate, and alkaline phosphatase (ALP) levels were measured by standard methods (Olympus AU600, Hamburg) in all laboratories. Vitamin D status, as determined by measurement of 25-hydroxyvitamin D (25-OHD), and intact parathyroid hormone (PTH) levels were determined by radioimmunoassay (ImmunoDiagnostic Systems, UK) and two site radioimmunoassay (Nicholl Institute Diagnostic Kit, USA), respectively, using commercially available diagnostic kits. Children with plasma 25-OHD levels less than 25 nmol/l (10 ng/ml) were considered to have vitamin D deficiency. The normal range for PTH is 1.1–6.8 pmol/l. The presence or absence of radiological evidence of rickets was determined from routine radiological reports.

The diagnosis of rickets was based on a combination of clinical findings (bow legs, rickety rosary, bone pain or deformity, tetany, convulsions due to hypocalcaemia), radiological evidence, biochemistry results (raised alkaline phosphatase with or without raised PTH) or low serum 25-OHD level, with a positive response to treatment with oral vitamin D and calcium supplementation. Children with hepatic or renal abnormality or on anticonvulsant therapy (including one who had concomitant vitamin D deficiency) were excluded from the study. Data were entered into Microsoft Excel and statistical analysis was performed using Stata, version 7.0.

RESULTS

A total of 65 children were identified with vitamin D deficiency rickets during the study period. Two other children with renal tubular rickets were excluded. Thirty nine children were of Asian origin, 24 Afro-Caribbean, and two Eastern European. There was little difference in the characteristics of children diagnosed in the two London regions, apart from the observation that 13/19 of children at King’s College Hospital were Afro-Caribbean compared to 10/46 presenting to the north London hospitals, while 36/46 of children presenting to...
the latter hospitals were Asian compared to 3/19 at King’s College Hospital. There were 37 (45%) males.

Almost half the children (29/65; 45%) presented with symptoms of hypocalcaemia (table 1). The remainder presented with symptoms and signs of bony rickets (fig 1). There was no difference in sex for the two modes of presentation. The 25-OHD concentrations of the patients are shown in table 2. All had concentrations below 15 nmol/l.

Children presenting with hypocalcaemic symptoms had significantly lower median calcium and alkaline phosphatase levels, and higher median phosphate levels, but there was no significant difference in PTH levels (table 2). Only 12/29 (41%) children presenting with hypocalcaemic symptoms had radiological evidence of rickets compared to 35/36 (97%) who did not (one girl with Neiman-Pick type C disorder was incidentally discovered to have hypocalcaemia secondary to nutritional vitamin D deficiency on routine blood tests with no radiological evidence of rickets; she successfully responded to treatment with oral vitamin D).

The most striking difference between the two modes of presentation was the age distribution (fig 2).15 Children presenting with hypocalcaemic symptoms had radiological evidence of rickets compared to 35/36 (97%) who did not (one girl with Neiman-Pick type C disorder was incidentally discovered to have hypocalcaemia secondary to nutritional vitamin D deficiency on routine blood tests with no radiological evidence of rickets; she successfully responded to treatment with oral vitamin D).

The most striking difference between the two modes of presentation was the age distribution (fig 2).15 Children presenting with hypocalcaemic symptoms were exclusively either under 3 or over 10 years of age. In particular, 9 of 11 (82%) infants under the age of 6 months, 16 of 23 (70%) under 1 year, and all seven children over the age of 10 years presented with hypocalcaemic symptoms. In contrast, vitamin D deficiency manifest as rickets without symptomatic hypocalcaemia, presented across the range of prepubertal ages, with the majority under 3 years of age.

Both modes of presentation occurred at all months of the year, but children presenting with hypocalcaemia showed a peak in the months following winter (March to July), while children with rickets presented almost equally throughout the year (fig 3). All children responded to treatment with vitamin D and their biochemical abnormalities returned to normal. One child with coeliac disease responded to a gluten-free diet with vitamin D supplementation.

**DISCUSSION**

In the absence of any renal tubular disorder or defect in vitamin D metabolism, vitamin D deficiency usually results from what is usually referred to as nutritional deficiency. Rickets may also occur as a result of calcium deficiency14 and this could possibly have been an additional factor in our patients. However, since vitamin D is principally derived from the action of sunlight on exposed skin, and darker skinned individuals require more exposure to sunlight than lighter skinned individuals to manufacture adequate vitamin D,15 any deficiency must be made up from dietary sources. Consequently, although vitamin D deficiency should strictly be regarded as a failure of adequate sunlight exposure,14 it is usually referred to as being “nutritional”.

In young infants, maternal vitamin D deficiency resulting in poor materno-fetal transfer of vitamin D during pregnancy and prolonged breast feeding are added risk factors. High phytic acid dietary content among some Asian children, particularly those whose diet contains a high proportion of chapattis, may also be an important aetiological factor,16 contributing to both vitamin D and calcium deficiency.

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**Table 1** Main presenting complaints among the 65 children with vitamin D deficiency

<table>
<thead>
<tr>
<th>Hypocalcaemic symptoms (n = 29)</th>
<th>n</th>
<th>No hypocalcaemic symptoms (n = 36)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsions</td>
<td>16</td>
<td>Incidental</td>
<td>11</td>
</tr>
<tr>
<td>Neuromuscular irritability</td>
<td>9</td>
<td>Bow legs</td>
<td>10</td>
</tr>
<tr>
<td>Apnoea</td>
<td>3</td>
<td>Bone pain</td>
<td>4</td>
</tr>
<tr>
<td>Stridor</td>
<td>1</td>
<td>Swollen joints</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone abnormality</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor delay</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short stature</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening family member</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2** A comparison of children presenting with and without hypocalcaemic symptoms

<table>
<thead>
<tr>
<th></th>
<th>Hypocalcaemic symptoms (n = 29)</th>
<th>No hypocalcaemic symptoms (n = 36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca2+ (mmol/l)</td>
<td>1.36 (0.84–2.08)</td>
<td>2.11 (1.32–2.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PO4 (mmol/l)</td>
<td>1.57 (0.85–3.16)</td>
<td>0.87 (0.38–4.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>989 (266–4393)</td>
<td>1723 (358–8988)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>25-OHD (nmol/l)</td>
<td>5.0 (2.1–14)</td>
<td>6.7 (2.7–14)</td>
<td>0.48</td>
</tr>
<tr>
<td>PTH (pmol/l)*</td>
<td>177 (22–760)</td>
<td>258 (21–640)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Results presented as median (range).

*Parathyroid hormone levels were only available for 18 and 14 children with and without hypocalcaemic symptoms, respectively (normal range: 1.1–6.8 pmol/l).

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**Figure 1** (A) Radiograph of patient aged 1 year with severe rickets. (B) Radiograph of patient aged 11 years presenting with hypocalcaemic symptoms and no radiological evidence of rickets.

**Figure 2** Age of children with vitamin D deficiency presenting with (dark bars) and without (light bars) hypocalcaemic symptoms. Growth velocity lines12 for boys (solid line) and girls (dotted line) have been superimposed onto the graph.
This theory is consistent with the significantly higher ALP levels and asymptomatic hypocalcaemia or normocalcaemia in children who presented with rickets. In these children, a lower metabolic demand for calcium would result in a more chronic course of disease, poor mineralisation of new bone, and increasing osteomalacia. On the other hand, the high metabolic demand for calcium in children presenting with hypocalcaemic symptoms results in a more acute presentation, before radiological evidence of rickets can occur.

Another explanation for the hypocalcaemia observed is that children with vitamin D deficiency and high levels of PTH become PTH resistant and, therefore, remain hypocalcaemic. However, although PTH resistance is a feature of vitamin D deficiency, this is unlikely to be the explanation for the differences seen because children presenting with hypocalcaemic symptoms had lower median PTH levels, although this was not statistically significant (table 2). However, it would help to explain the hyperphosphataemia seen in these patients.

The proportion of children with vitamin D deficiency presenting with hypocalcaemia in our study (45%) is higher than other reports. Narchi’s group, for example, reported that only 12/21 (57%) adolescents aged 10–15 years presented with hypocalcaemic symptoms in contrast to 7/7 (100%) in our study; and 2/18 (11%) children 5–25 months of age reported by Kreiter’s group presented with hypocalcaemia compared to 13/39 (33%) children in the same age group in our study. This is probably because many high risk children (dark skinned, prolonged breast feeding, maternal vitamin D deficiency) and mild cases of rickets are usually treated with vitamin D supplements by the general practitioner in the community or paediatric outpatient clinics. In contrast, children with hypocalcaemic symptoms are more likely to present to the hospital and be admitted for investigation and treatment.

Conclusion
Vitamin D deficiency has clearly re-emerged as a problem in the UK, especially in “at risk” ethnic minority groups. A significant number of children with vitamin D deficiency present with symptoms of hypocalcaemia with no radiological evidence of rickets. This is an under-recognised feature of vitamin D deficiency. Infants, toddlers, and adolescents are at particularly high risk, probably through the increased metabolic demand of rapid growth during these periods. Vitamin D deficiency should always be considered the likeliest cause of hypocalcaemia in these groups. This study emphasises the importance of vitamin D supplementation, not only in at risk infants but also in adolescents.

Authors’ affiliations
S Ladhani, L Srinivasan, J Allgrove, Department of Paediatrics, Newham General Hospital, London, UK
C Buchanan, Department of Paediatrics, King’s College Hospital, London, UK

REFERENCES
Angioinvasive aspergillosis

Following chemotherapy for leukaemia, a 6 year old girl developed multiple necrotic mucosal and skin lesions from which Aspergillus flavus was cultured. A chest radiograph (fig 1) revealed bilateral consolidation attributed to either alveolar haemorrhage or aspergillosis. A subsequent computed tomography (CT) scan (fig 2) revealed central cavitation and a unilateral pneumothorax. Invasive aspergillosis initial cavitation, thin ground glass haloes and small pneumothoraces are better detected by CT scan.1

V K T Nootigattu, J Sundaram, A Shabbani, S D Playfor
Royal Manchester Children’s Hospital, Manchester, UK; ntirupatayya@yahoo.com

Reference