Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study

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Vitamin D is crucial for skeletal development, and vitamin D deficiency can lead to rickets, poor linear growth, motor delay, bone fragility and hypocalcaemic seizures.[1-3] Most vitamin D is synthesised in the skin after exposure to ultraviolet B rays from direct sunlight, with dietary sources contributing little.[3,4] Vitamin D deficiency and associated rickets are re-emerging as major public health issues worldwide, including in Australia.

Accepted definitions of vitamin D deficiency are: mild, 25-hydroxyvitamin D (25OHD) level 25.1–50.0 nmol/L; moderate, 12.5–25.0 nmol/L; and severe, less than 12.5 nmol/L.[1] When vitamin D deficiency is associated with increased bone turnover, alkaline phosphatase level is elevated (biochemical rickets). In growing bone, features of radiological rickets include widening of the growth plate, and metaphyseal splaying and cupping. Our study aimed to assess vitamin D deficiency with rickets, rather than vitamin D deficiency alone.

We aimed to estimate the incidence of vitamin D deficiency rickets among children aged 15 years and younger living in Australia, and to describe factors associated with vitamin D deficiency rickets. We used national prospectively collected data with active reporting by paediatricians and child health specialists to the Australian Paediatric Surveillance Unit (APSU).

Methods

The APSU facilitates a national active surveillance system for rare childhood conditions, with about 1260 reporting clinicians (84% paediatricians).[5] Monthly report cards are returned with a response rate greater than 95%.[5] Vitamin D deficiency rickets was studied from January 2006 to July 2007.

All case notifications were followed up via questionnaire to obtain demographic, clinical and biochemical data. Pregnancy, birth and breastfeeding data were collected for children younger than 3 years of age. Inclusion criteria were: children aged ≤ 15 years with vitamin D deficiency rickets (25OHD ≤ 50 nmol/L, and elevated alkaline phosphatase levels as per local pathology service reference values and/or radiological rickets). Exclusion criteria were vitamin D deficiency rickets associated with an underlying chronic disease and all genetic forms of rickets. Data were collated by APSU staff and reviewed by a paediatric endocrinologist (CFM). Socioeconomic status was estimated using the Socio-Economic Indexes For Areas (SEIFA).[6] Ethics approval was granted by the Human Research Ethics Committee of the Children's Hospital at Westmead.

Statistical analysis

Data were analysed and assessed for normality using SPSS, version 18 (IBM, Armonk, NY, USA). Descriptive data are presented as mean (SD) or median (range). Differences between groups were assessed using the Mann–Whitney U test (two groups) or the Kruskal–Wallis test (three groups). Association between length of breastfeeding and serum 25OHD level was assessed using Spearman rank correlation (coefficient denoted as ρ). Australian state-based population figures for children < 15 years, which were age- and sex-standardised,[7] were used to estimate the incidence of simple vitamin D deficiency per year. Comparisons of incidences was performed using the StatXact, version 4 (Cytel Inc, Cambridge, Mass, USA) difference in two binomial proportions test (asymptotic method).

Results

Between January 2006 and July 2007, there were 851 notifications of vitamin

Abstract

Objective: To determine the incidence of and factors associated with vitamin D deficiency rickets in Australian children.

Design: 18-month questionnaire-based prospective observational study, using Australian Paediatric Surveillance Unit (APSU) data.

Setting: Australian paediatricians and child health workers, January 2006 – July 2007.

Participants: Children aged ≤ 15 years with vitamin D deficiency rickets (25-hydroxyvitamin D [25OHD] ≤ 50 nmol/L, and elevated alkaline phosphatase levels [> 229 IU/L] and/or radiological rickets).

Main outcome measures: Incidence of vitamin D deficiency rickets. Description of demographics, clinical presentation, identification and further analysis of overrepresented groups, and treatment regimens compared with best-practice guidelines.

Results: We identified 398 children with vitamin D deficiency (55% male; median age, 6.3 years [range, 0.2–15 years]). The overall incidence in children ≤ 15 years of age in Australia was 4.9/100 000/year. All had a low 25OHD level (median, 28 nmol/L [range, 5–50 nmol]) and an elevated alkaline phosphatase level (median, 407 IU/L [range, 229–5443 IU/L]), and 48 (12%) were hypocalcaemic. Ninety-five children had wrist x-rays, of whom 67 (71%) had rachitic changes. Most (98%) had dark or intermediate skin colour and 18% of girls were partially or completely veiled. Most children were born in Africa (252; 63%) and 75% of children were refugees. Duration of exclusive breastfeeding was inversely related to serum vitamin D levels in children < 3 years of age. Empirical vitamin D treatment was given to 4% of children before diagnosis.

Conclusions: Vitamin D deficiency rickets is a significant problem in Australia among known high-risk groups. Public health campaigns to prevent, identify and treat vitamin D deficiency, especially in high-risk groups, are essential.

D deficiency rickets to the APSU; 453 of these were either duplicate notifications or did not meet the inclusion criteria. Of the remaining 398 children (219 [55%] male; median age, 6.3 years [range, 0.2–15 years]), 36 (9%) were classified as having severe vitamin D deficiency, 155 (39%) as moderate and 207 (52%) as mild.

The estimated national annual incidence of vitamin D deficiency rickets among children was 4.9/100 000 children (95% CI, 4.4–5.4/100 000). There were 251 children from Victoria, or 13.0/100 000 per year (95% CI, 11.3–14.6/100 000; $P < 0.001$); and 69 from Western Australia, or 8.4/100 000 (95% CI, 6.5–10.6/100 000; $P < 0.001$). The annual incidence for New South Wales was significantly lower than the national incidence: 70 children, or 2.6/100 000 (95% CI, 2.0–3.3/100 000; $P < 0.001$). There were eight cases from South Australia, Queensland, the Northern Territory, the Australian Capital Territory and Tasmania. The median age at diagnosis was 6.24 years (range, 0.1–15.0 years) and there was a small difference in annual incidence (standardised difference: – 1.3/100 000; $P < 0.05$) between children aged 0–4 years (153 children; incidence, 5.9/100 000 [95% CI, 4.9–6.9/100 000]) and children aged 5–14 years (245 children; incidence, 4.5/100 000 [95% CI, 3.9–5.1/100 000]). Postcode data were available for 371 children. Children were evenly distributed in areas of relative socioeconomic disadvantage (SEIFA 1–5, 179 [48%]) and advantage (SEIFA 6–10, 192 [52%]). Most patients (297; 75%) were refugees, and vitamin D deficiency rickets was most commonly detected by abnormal biochemical results on routine screening through refugee clinics.

The presenting symptoms are summarised in Box 1. Biochemical features are outlined in Box 2. Data from wrist x-rays were available for 95 children, of whom 67 (71%) showed radiological rickets. The median 25OHD level was not statistically different between cases with radiological rickets, 18 nmol/L (range, 5–45 nmol/L), and those without, 20 nmol/L (range, 8–45 nmol/L) ($P = 0.074$).

Presentation demonstrated a seasonal variation, with 240 cases (60%) identified in winter and spring, compared with 158 (40%) in summer and autumn (Box 3).

Nine children had been born prematurely. Breastfeeding data were collected for 96 of the 134 children who were younger than 3 years of age at diagnosis. The median duration of exclusive breastfeeding was 6.0 months (range, 1.5–24.0 months), with an inverse association between the length of time of exclusive breastfeeding and serum 25OHD ($\rho = – 0.20$, $P = 0.05$).

Most patients were born in Africa (252; 63%), and 94 (24%) were born in Australia (Box 4). Skin colour of mothers was similar to those reported for children, which were "dark" in 85%, "intermediate" in 13% and "fair" in 2%. One hundred and forty-two children (36%) and almost half the children's parents (47%) were born in Sudan. The annual incidence for patients of Sudanese background was estimated to be 2300/100 000 — 350 times greater than the national estimated incidence.

One hundred and four of 338 (31%) mothers were veiled during pregnancy. Mothers who reported being consistently covered during pregnancy (30/104) had children with lower median serum concentrations of 25OHD at diagnosis than mothers who reported inconsistent covering (74/104) (consistently veiled, median, 22 nmol/L [range, 9–42 nmol/L] v inconsistently veiled, median 29 nmol/L [range, 10–47 nmol/L]; $P = 0.001$), and their children were diagnosed at an earlier age (consistently veiled, median, 2.7 years [range, 2 months – 12 years] v inconsistently veiled, median 7.4 years [1 month – 15 years]; $P = 0.001$). There was no difference between those who reported intermittent covering and those who were uncovered.

Data on veiling were available for 158/179 girls (88%); 29 were veiled (18%) and 129 not veiled (82%); there was no difference in median 25OHD levels (veiled, 28 nmol/L [range, 9–47 nmol/L] v non-veiled, 26 nmol/L [10–47 nmol/L]; $P = 0.70$).

Treatment after diagnosis was recorded for 361 children (91%); 216 children were administered intermittent megadose ("stoss") vitamin D therapy, 75 000–150 000 units per dose, repeated up to three times, and 145 patients used daily dosing regimens of 800–5000 units daily. Total vitamin D dose administered to all children was between 72 000 and 450 000 units over the treatment course. Empirical vitamin D treatment was given to 4% of children before diagnosis.

Discussion

This is the first study to assess the incidence of vitamin D deficiency rickets in Australian children. Our data confirmed that recent migrants, especially those with dark skin, had a significantly higher incidence of vitamin D deficiency rickets than the overall Australian paediatric population. Sudan was the most common country of birth for children and parents in this study, which reflected the targeted humanitarian refugee intake into Australia over the study period.[8]

1 Reason for presentation of cases identified with simple vitamin D deficiency rickets
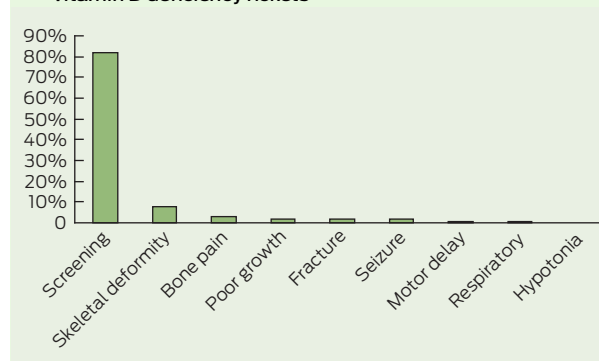
2 Biochemical analysis of children identified with simple vitamin D deficiency

	No. of children	Reference range	Median (range)	Above/below cut point, no. (%)
25-hydroxyvitamin D, nmol/L	398	> 50	28 (5–50)	398 (100%)
Alkaline phosphatase, IU/L	393	80–325*	407 (229–5443)	398 (100%)
Calcium, mmol/L	358	2.10–2.65	2.38 (1.22–2.94)	48 (12%)
Phosphorus, mmol/L	328	1.00–1.80	1.69 (0.16–2.78)	28 (7%)
Parathyroid hormone, pmol/L	170	1.0–7.0	6.85 (0.8–99.1)	195 (49%)

* Quoted reference range for the Children's Hospital at Westmead laboratory. Local laboratory quoted reference ranges varied, leading to 100% incidence of elevated alkaline phosphatase levels. ◆

Seasonal variation was observed, with increased incidence in late winter/spring that decreased over summer. The effect of latitude was also important, with Victoria's reported incidence nearly five times that of NSW. The populations at risk are likely to differ between states and regions, which may also effect reporting rates.

Maternal vitamin D deficiency has been shown to be a risk factor for deficiency in infants,[9] and we found that consistent veiling among mothers was associated with more severe vitamin D deficiency and earlier presentation of paediatric vitamin D deficiency. These data support the current recommendations that women of childbearing age who are at risk of vitamin D deficiency should have routine vitamin D screening during

pregnancy and receive appropriate supplementation.[1] Breast milk is widely recognised as the most appropriate food for babies, but it contains very little vitamin D,[10] and prolonged breastfeeding is associated with vitamin D deficiency rickets.[11] However, most cases were in children over 5 years of age.

Although our study provides the first national estimate of vitamin D deficiency rickets, it is likely that there was underreporting of cases leading to an underestimate of the true incidence of vitamin D deficiency rickets. Another limitation is that the sample analysed may be biased, given that most cases were reported from services such as refugee health clinics with an increased awareness of the importance of vitamin D deficiency rickets and routine screening protocols. Further, there is significant variation observed between commercially available vitamin D assays.[12]
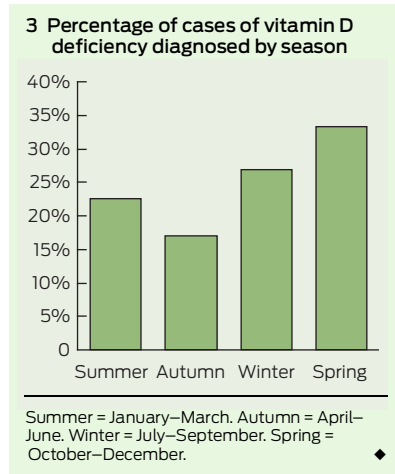
Soon after the commencement of this study, an Australian and New Zealand consensus statement on the prevention and treatment of infant and childhood vitamin D deficiency was published.[1] Although the vast majority of children in our study received vitamin D therapy within the recommended guidelines to treat established rickets,[1] attention to routine screening and supplementation to prevent vitamin D deficiency are required. Further public health campaigns are

also needed to increase awareness of vitamin D deficiency in at-risk groups.

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3 Percentage of cases of vitamin D deficiency diagnosed by season

Summer = January–March. Autumn = April–June. Winter = July–September. Spring = October–December.

4 Country of birth of children with vitamin D deficiency rickets and their parents

Child's country of birth	No. of children (%)	Parents' country of birth*	No. of parents (%)
Sudan	142 (35.9)	Sudan	363 (47.3)
Australia	94 (23.6)	Somalia	98 (12.8)
Egypt	31 (7.7)	Ethiopia	44 (5.7)
Kenya	28 (6.9)	Eritrea	34 (4.4)
Ethiopia	20 (4.9)	Afghanistan	22 (2.9)
Tanzania	13 (3.1)	India	20 (2.6)
Somalia	11 (2.8)	Burundi	18 (2.3)
Burma	7 (1.8)	Kenya	18 (2.3)
Afghanistan	5 (1.3)	Liberia	17 (2.2)
Congo	5 (1.3)	Burma	16 (2.1)
Eritrea	4 (1.0)	Congo	15 (2.0)
Uganda	4 (1.0)	Australia	11 (1.4)
Thailand	4 (1.0)	Pakistan	9 (1.2)
Other (13 Africa)	30 (7.7)	Other (9 Africa)	82 (10.7)
Total	398 (100)	Total	767

* Data available on 385 mothers and 382 fathers.