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Vitamin D Deficiency and Sudden Unexpected Death in Infancy and Childhood: A Cohort Study

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ABSTRACT

We sought to (1) determine if there is an increased prevalence of vitamin D deficiency (VDD) in cases of sudden death in infancy and childhood; (2) establish whether there is a link between VDD and infection; and (3) assess if the level of vitamin D can be related to abnormalities in the skeletal survey and rib histology in our cohort. The postmortem reports of cases in which vitamin D levels were measured in 2009 and 2010 were retrieved. When parental consent for audit had been granted, rib histology and skeletal surveys were reviewed. Plasma 25-hydroxyvitamin D levels were measured in 41 postmortem cases. Ten (24.5%) had adequate levels, 5 (12%) had suboptimal levels, 16 (39%) had moderate deficiency, and 10 (24.5%) had severe deficiency. We had only 4 cases with VDD and infection. There were 25 cases of unexplained death in our cohort, and 76% of these had inadequate vitamin D levels. The rib histology was abnormal in 69% of cases that had inadequate vitamin D levels, while the radiology was abnormal in 19% of cases. A significant proportion of infants and children who died suddenly and unexpectedly had inadequate levels of vitamin D. We were unable to confirm or exclude an association between VDD and infection due to the small number of cases with confirmed infection. Further multicenter studies are needed to confirm our findings and explore possible associations between VDD and other known risk factors for sudden unexplaineddeath in infancy and childhood.

Key words: rickets, SIDS, sudden unexplained death, vitamin D deficiency

INTRODUCTION

Vitamin D functions as a hormone essential for the maintenance of the musculoskeletal system [1–3]. It also has important immune-modulating functions [3,4] and regulates 3% of the human genome [5]. Therefore, vitamin D deficiency (VDD) has wide-ranging effects beyond rickets in children and osteomalacia in adults. It is now believed that VDD is a risk factor for the development of cardiovascular disease, diabetes mellitus, infection, multiple sclerosis, and some forms of cancer [1,4–6].

There are increasing reports of a resurgence of VDD in children, both in the United Kingdom and worldwide [1,2,4,5,7–13]. Callaghan and colleagues [14] reported an overall incidence in the United Kingdom of 7.5 per 100 000 children in 2006. More recently, reported prevalence, as estimated by measuring plasma 25-hydroxyvitamin D (25-OHD) concentration, ranges from 29% to 40% [4,7,8]. In a population study of young people aged 4 to 18 years in Great Britain, Absoud and colleagues [4] found that 35% of the participants had vitamin D insufficiency (levels <50 nmol/L). A U.S. study found that 12% of healthy infants and toddlers have VDD and 40% have levels below the accepted optimal threshold (insufficiency) [10]. Comparable results were reported in other countries, including Canada [2], Turkey [12], and South Korea [13].

There is recent evidence suggesting that VDD is associated with increased mortality rates in adults [6,15]. It may also be associated with sudden infant death syndrome (SIDS) [16].

The measurement of vitamin D levels was introduced as part of the Sheffield protocol for investigating SIDS and sudden unexplained death in childhood (SUDC) in 2009, whenever enough blood for the assay could be procured after samples for the essential investigations in the protocol (microbiology, toxicology, and acylcarnitine measurement) were obtained. We carried out a service evaluation to assess if this test adds any value to our investigation. In particular, we wanted to determine if there is an increased prevalence of VDD in cases of SIDS or SUDC, if there is a link between VDD and infection, and finally if the level of vitamin D can be related to the

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Table 1. Demographic features, cause of death, vitamin D levels, skeletal survey findings, and microbiology results of the cohort

Case	Age	Sex	Race	Cause of death	25-OHD levels (nmol/L)[a]	Skeletal survey (reported before the PM)	Microbiology findings	PM interval
1	5m	F	White	Hypoxic ischaemic encephalopathy	83.5	Normal	Negative	1d
2	4m	M	White	Acute sepsis	88.8	Normal	Klebsiella in blood and CSF and in brain and bronchial swabs	1d
3	2y	M	White	SUDC	77.9	Normal	PM flora	1d
4	6m	M	White	SIDS	130.3	Normal	Negative	3d
5	2m	M	White	Hypoxic ischaemic encephalopathy	77.6	Normal	Negative	1d
6	2w	M	White	SIDS	79.2	Normal	Negative	1d
7	13m	M	White	SUDC	104.4	Normal	Negative	3d
8	18m	M	White	SUDC	78.9	Normal	Negative	1d
9	13m	M	White	Bronchopneumonia	75.1	Normal	*Haemophilus influenzae* in bronchial and middle ear swabs	2d
10	18w	F	White	SIDS	115.9	Normal	PM flora	5d
11	10w	M	White	SIDS	62.2	Normal	*H. influenzae* in middle ear, nasopharynx, and bronchial swabs	4d
12	10m	F	White	SIDS	62.9	Normal	Negative	2d
13	4w	F	White	SIDS	59.3	Normal	PM flora	1d
14	4m	M	White	SIDS	65.4	Normal	PM flora	1d
15	5m	M	White	Bronchopneumonia	59	Normal	Negative	2d
16	5.5m	F	Asian	Acute on chronic myocardial damage	32.5	Normal	Negative	1d
17	7w	F	White	SIDS	42.6	Normal	PM flora	1d
18	7w	M	White	SIDS	35.5	Normal	Negative	1d
19	14m	M	White	Aspiration of gastric contents	43.3	Normal	Negative	1d
20	3m	M	White	SIDS	33.9	Normal	PM flora	1d
21	9w	F	White	SIDS	33	Normal	PM flora	2d
22	14y	M	White	SUDEP	31	Normal	PM flora	5d
23	4.5m	M	White	SIDS	48.1	Normal	PM flora	2d
24	6w	M	White	SIDS	47	Normal	Normal flora	2d
25	7w	F	White	SIDS	36.6	Normal	Negative	1d
26	6m	F	White	Complex syndrome of uncertain genetic classification	41.7	Cupped and frayed metaphyses	PM flora	1d
27	11m	M	White	Hypoxic ischaemic encephalopathy after near drowning	41.3	Normal	Negative	1d
28	3m	M	AC	SIDS	38.2	Normal	Negative	2d
29	2y	M	Asian	Heart failure secondary to complex cardiac malformation	46.6	Diffuse osteoporosis	Negative	1d
30	28m	F	White	SUDC	29.4	Normal	*Streptococcus pneumoniae* in bronchial, throat and nasal swabs	1d
31	3y	M	White	Cardiac arrhythmia secondary to complex congenital heart disease (operated)	29.4	Normal	Negative	4d
32	11m	F	White	SIDS	15.9	Normal	PM flora	1d
33	15w	M	White	SIDS	14.2	Normal	Negative	8h

Table 1. Continued

Case	Age	Sex	Race	Cause of death	25-OHD levels (nmol/L)[a]	Skeletal survey (reported before the PM)	Microbiology findings	PM interval
34	3m	F	White	Heart failure secondary to subendocardial fibroelastosis	17.4	Normal	Negative	2d
35	30d	M	White	SIDS	22.2	Normal	Negative	1d
36	19m	F	Asian	Bronchopneumonia	14.3	Normal	Negative	3d
37	7y	F	White	Diabetic ketoacidosis	20.7	Reduction in bone density	Negative	4d
38	12y	M	White	Hypertrophic cardiomyopathy secondary to DMD	15.1	Overtubulated bones due to DMD	Negative	2d
38	9d	M	White	SIDS	7.5	Normal	Normal flora	4d
40	9h	M	White	Complex cardiac malformation	17.4	Normal	Negative	1d
41	4y	F	White	SUDEP	<6.0	Normal	PM flora	2d

25-OHD indicates 25 hydroxyvitamin D; PM, postmortem; m, month; w, week; y, year, F, female; M, male; d, day; h, hour; CSF, cerebrospinal fluid; AC, afro-Caribbean; SIDS, sudden infant death syndrome; SUDC, sudden unexplained death in childhood; SUDEP, sudden unexpected death in epilepsy; DMD, Duchenne muscular dystrophy.

[a]A 25-OHD level of <25 nmol/L was considered severely deficient, a level between 25 and 50 nmol/L moderately deficient, 50–75 nmol/L suboptimal, and > 75 nmol/L adequate.

presence of abnormalities in the skeletal survey and rib histology in our cohort.

MATERIAL AND METHODS

The postmortem reports of cases in which vitamin D levels were measured in 2009 and 2010 were retrieved from the archives of the histopathology department at Sheffield Children's Hospital. The following parameters were recorded on an anonymized excel spreadsheet: age, sex, race, cause of death, postmortem serum vitamin D levels, skeletal survey findings, and microbiology results.

In those cases in which parental consent for audit had been granted, the histology of the rib was reviewed blindly by 2 pediatric histopathologists (M.C.C. and M.A.) and the full skeletal survey was reviewed blindly by 2 pediatric radiologists (A.O. and A.S.).

The rib histology assessed the presence or absence of the histologic features of rickets/VDD described in the literature: widening of the metaphysis (also known as cupping of the costochondral junction, especially in the radiology literature), thickening of the growth plate with expansion of the cartilage matrix in the primary spongiosa and metaphysis, blood vessels penetrating the growth plate, and abnormal trabeculae in the shaft of the rib. The latter was defined as the presence of rather thickened trabeculae showing a core of woven bone with persistent mineralized cartilage [17–19].

The radiologic review assessed bone density (normal or reduced), trabecular markings, and presence or absence of the radiologic signs of rickets. For the purposes of this analysis and as stated in the report received from the chemical pathology laboratory, a 25-OHD level of < 25 nmol/L was considered severely deficient, a level between 25 and 50 nmol/L moderately deficient, 50–75 nmol/L suboptimal, and >75 nmol/L adequate [20,21].

The study was registered as a service evaluation with the Trust's Clinical Governance Department (number SE178).

RESULTS

Vitamin D levels were requested in 45 postmortem evaluations. In 4 cases (9%), the sample was insufficient for analysis.

Table 1 shows the demographic features, cause of death, 25-OHD levels, skeletal survey findings (as reported by the ''duty'' consultant pediatric radiologist before conducting the postmortem examination), and the microbiology results in the 41 cases of our cohort. The age range was from 9 hours to 14 years, although 24 of 41 (58.5%) cases were ≤6 months of age. Twenty-seven cases (66%) were male and 14 female. Most patients were white (90%). The postmortem interval (time between death and the postmortem examination) ranged from 8 hours to 5 days (average 1.8 day).

Ten of 41 cases (24.5%) had adequate vitamin D levels, 5 (12%) had suboptimal levels, 16 (39%) had moderate deficiency, and 10 (24.5%) had severe deficiency. Suboptimal vitamin D levels, as well as moderate or severe deficiency, were present in all ages, but of particular interest is that it was seen in all of the patients more than 2 years of age ($n = 8$); the exception was case 3. Of the 26 cases that had moderate or severe deficiency, 15 (58%) were male and 11 female. All 4 non-white patients had VDD (3 moderate, 1 severe).

Of the 31 of 41 (76%) cases that had inadequate vitamin D levels, the cause of death was explained in 12 (39%) but remained unexplained in the remainder (19/31,

Table 2. Histologic findings in cases in which the rib sampled at postmortem was subsequently reviewed

Case	Vitamin D status	25-OHD levels (nmol/L)	Histology			
			Widening of metaphysis (cupping of costochondral junction)	Growth plate (including cartilage matrix)	Blood vessels penetrating growth plate	Abnormal trabeculae[a]
3	Adequate	77.9	No	Normal	No	No
4	Adequate	130.3	No	Normal	No	No
6	Adequate	79.2	No	Irregular	No	No
7	Adequate	104.4	No	Normal	No	No
8	Adequate	78.9	No	Normal	No	No
10	Adequate	115.9	No	Expanded[b]	Yes	Yes[b]
12	Suboptimal	62.9	Yes[b]	Expanded[c]	Yes	Yes[c]
14	Suboptimal	65.4	Normal	Normal	No	No
15	Suboptimal	59	Yes[b]	Expanded[b] disorganized	Yes	Yes[b]
17	Moderately deficient	42.6	Yes [c]	Expanded[c]	Yes	Yes[c]
19	Moderately deficient	43.3	No	Normal	No	No
20	Moderately deficient	33.9	Yes[c]	Disorganized	Yes	Yes[c]
21	Moderately deficient	33	Yes[c]	Disorganized and expanded[b]	Yes	Yes[b]
22	Moderately deficient	31	No	Normal	No	No
23	Moderately deficient	48.1	Yes[b]	Disorganized	Yes	Yes[b]
24	Moderately deficient	47	Yes[c]	Disorganized	Yes	Yes[c]
27	Moderately deficient	41.3	Yes[b]	Normal	No	Yes[b]
29	Moderately deficient	46.6	No	Normal	No	No
34	Severely deficient	17.4	Yes[b]	Expanded[b]	Yes	No
35	Severely deficient	22.2	Yes[c]	Disorganized and expanded[b]	Yes	Yes[c]
40	Severely deficient	17.4	Yes[d]	Expanded[c]	Yes	Yes[d]
41	Severely deficient	<6.0	No	Normal	No	No

25-OHD indicates 25 hydroxyvitamin D.
[a]Thickened trabeculae with a core of woven bone and increased osteoid deposition.
[b]Mild.
[c]Moderate.
[d]Marked.

61%). This suggests that VDD is more prevalent in the unexplained death group.

There were 4 cases that died because of an infection (confirmed histologically and/or microbiologically). One of these cases had severe VDD, 1 had suboptimal levels, and the other 2 had adequate levels. There were another 2 cases that had positive microbiologic findings that were considered contributory to the cause of death as opposed to the sole cause of death. One of these cases had suboptimal vitamin D levels and the other had moderate deficiency.

Twenty-five of 41 (61%) (16 male, 9 female) deaths in our cohort were unexplained. This group included 19 SIDS cases (all <12 months of age), 4 cases of SUDEC (all between 13 months and 28 months of age), and 2 cases of sudden unexpected death in epilepsy (4 and 14 years of age). Six of 25 cases (24%) had adequate levels, 4 (16%) had suboptimal levels, 10 (40%) had moderate deficiency, and 5 (20%) had severe deficiency. In the SIDS group (12 male, 7 female), 16 (84%) had vitamin D values below normal range: these included 4 cases (25%) with suboptimal levels of vitamin D, 8 (50%) with moderate deficiency, and 4 (25%) with severe deficiency.

The full skeletal survey was reported prospectively by pediatric radiologists before the postmortem examination. They were searching for abnormalities that might contribute to the autopsy (eg, fractures, dysplasia). They reported abnormalities in 4 cases (13%), all later found to have inadequate vitamin D levels (cases 26, 29, 37, and 38). Two cases with severe deficiency had reduced bone density and overtubulated bones. One of these was a child with Duchenne muscular dystrophy. Two cases with moderate deficiency had cupped and frayed metaphyses and diffuse osteoporosis. Apart from the Duchenne muscular dystrophy case, bone abnormalities were not suspected during life and only detected on postmortem imaging.

In 30 of 41 cases with consent for audit, the histology of the rib sampled at postmortem was reviewed. The histologic findings are shown in Table 2. The full skeletal survey was also retrospectively reviewed by 2 consultant pediatric radiologists assessing specifically for rickets (Table 3).

Table 3. Radiologic features in cases reviewed retrospectively by 2 pediatric radiologists after postmortem examination completion

			Radiologic features			
Case	Vitamin D status	25-OHD levels (nmol/L)	Density	Trabecular margins	Rickets	Other
3	Adequate	77.9	Reduced	N	R1: no	R1: slender bones, coxa valga, scoliosis
					R2: likely rickets	R2: platispondyly; mild porosis
4	Adequate	130.3	N	N	No	R1: mild cupping distal radius/ulna (within normal limits)
					No	R2: thin vertebral plates
6	Adequate	79.2	N	N	No	
7	Adequate	104.4	N	N	No	R2: coarse trabeculae
8	Adequate	78.9	N	N	No	
10	Adequate	115.9	N	N	R1: no R2: likely rickets[a]	R2: platispondyly Reduced bone density[a]
12	Suboptimal	62.9	N	N	No	
14	Suboptimal	65.4	N	N	No	
15	Suboptimal	59	N	N	No	
17	Moderately deficient	42.6	N	N	No	
19	Moderately deficient	43.3	N	N	No	
20	Moderately deficient	33.9	N	N	No	
21	Moderately deficient	33	Reduced	N	R1: no	R1: possible osteopenia; poor-quality external films
					R2: possibly rickets	R2: thin vault reduced density
22	Moderately deficient	31	N	N	No	R1: thick skull vault (neurologic deficit); fibrous cortical defect distal left femur
23	Moderately deficient	48.1	N	N	No	
24	Moderately deficient	47	N	N	No	
27	Moderately deficient	41.3	N	N	No	
29	Moderately deficient	46.6	Reduced	N	No	R1: wide metaphyses; no definite dysplasia
34	Severely deficient	17.4	N	N	No	
35	Severely deficient	22.2	N	N	No	
40	Severely deficient	17.4	N	N	No	
41	Severely deficient	<6.0	N	N	No	R1: growth arrest lines R2: growth arrest lines; thin end plates

25-OHD indicates 25 hydroxyvitamin D; N, normal; R1, radiologist 1; R2, radiologist 2.
[a]Abnormal radiology (R2) and abnormal histology in keeping with rickets but with adequate levels of vitamin D.

The rib histology was reviewed in 16 cases in which vitamin D levels were suboptimal or moderately or severely deficient. Abnormalities were identified in 11 (69%): there was widening of the metaphysis (cupping of the costochondral junction) in 11 (69%), thickening of the growth plate with expansion of the cartilage matrix in 7 (44%), penetrating vessels into the growth plate in 10 (62.5%), and abnormal trabeculae in 10 (62.5%) (Fig. 1). Of interest, 2 (cases 6 and 10) with adequate vitamin D levels showed abnormal features: case 6 had widening of the metaphysis and case 10 had thickening of the growth plate with penetrating vessels and abnormal trabeculae. Five of the 16 (31%) cases with suboptimal vitamin D levels or with VDD were histologically normal.

When the preautopsy radiology report and the subsequent review by 2 additional radiologists are considered together, 6 of 31 (19%) cases with suboptimal, moderate, or severe deficiency had radiologic abnormality. Reduced bone density was identified in cases 3, 21, and 29, and rickets was suspected in cases 10 and 21 by Radiologist 2 but not by Radiologist 1 (Table 3 and Figs. 2,3). Images of cases 26, 37, and 38 were not available for review due to consent issues.

DISCUSSION

Recently, there have been many studies confirming the high prevalence of VDD and insufficiency among children, both in the United Kingdom [1,4,7–9] and abroad [1,2,10–13]. We present the 1st report confirming these findings in a pediatric postmortem cohort in the United Kingdom. A PubMed search identified only 1

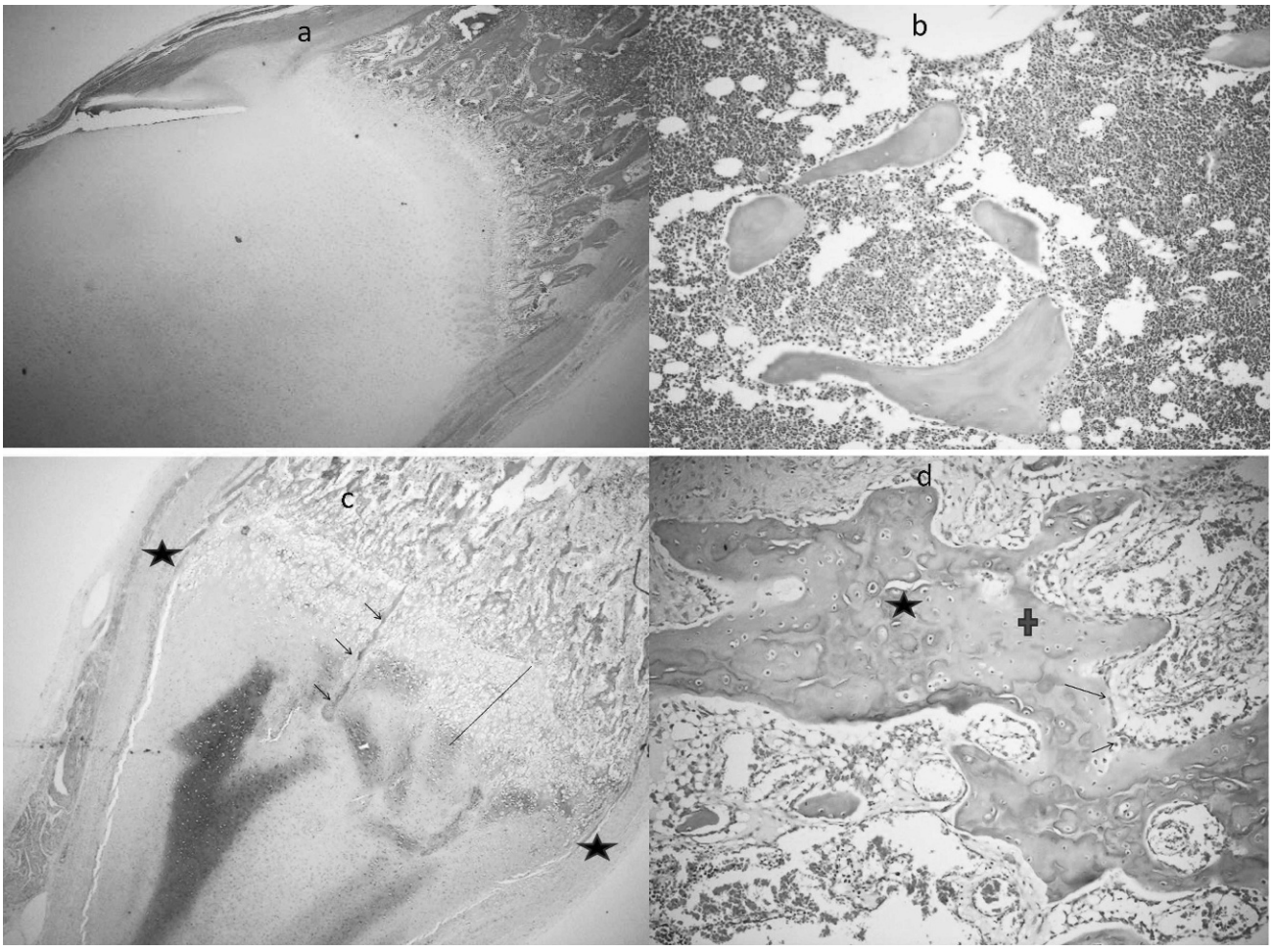

Figure 1. Rib histology showing (**a**) normal metaphyseal width and growth plate in a case with adequate levels of vitamin D (case 3, hematoxylin and eosin [H&E] stain ×4); (**b**) normal trabeculae showing lamellar bone (case 8, H&E stain, ×10); (**c**) increased metaphyseal width resulting in cupping of the costochondral junction (between ★), thickening of the growth plate with expansion of the cartilage matrix (marked with a line), and penetrating vessel into the cartilaginous growth plate (arrows) (case 21, moderate deficiency of vitamin D, H&E stain; ×4); and (**d**) abnormal thickened trabeculae with a core of woven bone (★), excess of osteoid (✚), and a rim of osteoblasts (arrows) (case 35, severe deficiency of vitamin D, H&E stain, ×20).

previous study in the English literature, which measured vitamin D concentrations in a group of infants at postmortem in the United States [16].

Serum 25-OHD levels are considered to be the best marker for vitamin D status. However, there is no absolute consensus on the optimal level of circulating 25-OHD, and different studies use different definitions for VDD, insufficiency, and sufficiency [1,2,4–8,10,20]. Levels <25 nmol/L have traditionally been regarded as VDD for both clinical practice and dietary reference values, and this level is associated with the development of rickets in children or osteomalacia in adults. Recently, many experts consider vitamin D levels <50 nmol/L as insufficient, and levels >75 nmol/L as optimal for bone health, calcium homeostasis, and reduction of the risk of cardiovascular disease, diabetes mellitus, multiple sclerosis, and mortality [2,5,6,8,10–13,20,21]. It would be helpful if uniform definitions were adopted both nationally and internationally so that different studies can be compared.

We have found that 75.5% of our cohort had inadequate vitamin D levels (<75 nmol/L). Even if we take a level of 50 nmol/L as the cut-off, the prevalence remains significant (63.5%). Either of these figures is higher than the reported prevalence in living children in the United Kingdom [1,4,7–9]. Possible explanations for this difference include the fact that this is a postmortem study and that our cohort, by definition, is a select group that may not be representative of the general pediatric population. In addition, although 25-OHD is stable in the serum [16], a degree of postmortem degradation/breakdown in some cases cannot be entirely excluded. Another possible factor is that 10 of our cases with inadequate vitamin D levels (32%) had a chronic medical condition and/or were ill in hospital prior to death, which might have led to a lower vitamin D level.

Similar to previous studies [2,4,7,8], inadequate vitamin D levels were present in all ages and the prevalence seemed to increase with age. As probably

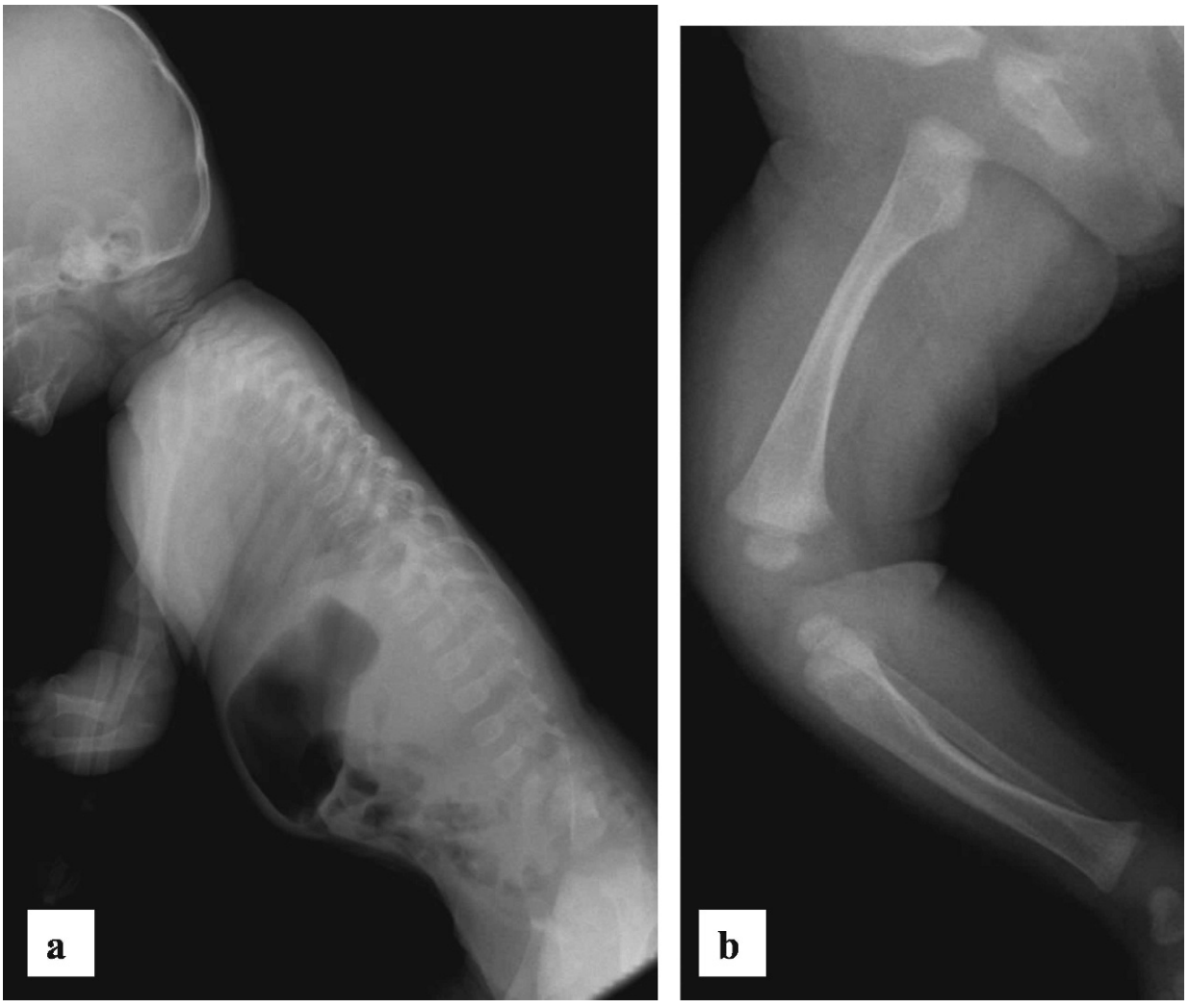

Figure 2. Radiographs of case 10. **a.** Lateral spine radiograph shows osteoporosis and loss of height of thoracic vertebral bodies. **b.** No metaphyseal changes to suggest active rickets. No definite cause for this patient's osteoporosis was identified.

expected, all of our non-white patients had VDD. However, the majority of the patients with inadequate vitamin D levels were white (87%). This is in line with the findings in living children that non-white children are more vulnerable, but the problem of VDD is now seen across the community [2,4,8,9].

Vitamin D has important immune-modulating functions [3,22]. Therefore, it is thought that VDD is a risk factor for infection, especially in the respiratory system. We could not confirm or exclude an association between inadequate vitamin D levels and increased risk of infection in our cohort because we only had 4 cases of confirmed infection.

Sudden infant death syndrome is defined as the sudden unexpected death of an infant younger than 1 year, with onset of the fatal episode apparently during sleep, which remains unexplained after a thorough investigation, including a complete autopsy, examination of the death scene, and review of the clinical history [23]. Following the fall in the incidence of SIDS as a result of the ''back to sleep'' campaign, the incidence has since remained static. The Triple risk model for SIDS proposes that SIDS occurs in a vulnerable infant during a critical period of development if an exogenous stress factor is present [24].

Possible external stress factors include infection and nutritional deficiencies, such as VDD. It has been previously hypothesized that thiamine deficiency [25] and vitamin E/selenium deficiency [26] may be associated with SIDS. In 1971, Kraus and colleagues put forward a theory suggesting that VDD might explain some of the cases of SIDS based on the observation that SIDS occurs more commonly in the winter months and that SIDS infants spent less time outdoors compared with control infants [23]. An epidemiologic study in Scandinavia has found an association between vitamin A deficiency and SIDS [27]. However, none of these hypotheses and epidemiologic findings was confirmed by measuring vitamin levels in SIDS cases.

In the only study measuring vitamin D (25-OHD) levels in SIDS cases at postmortem, Hillman and colleagues [16] found that the mean ± SD of serum 25-OHD levels in 31 SIDS cases (19.0 ± 7.9 ng/mL) was not

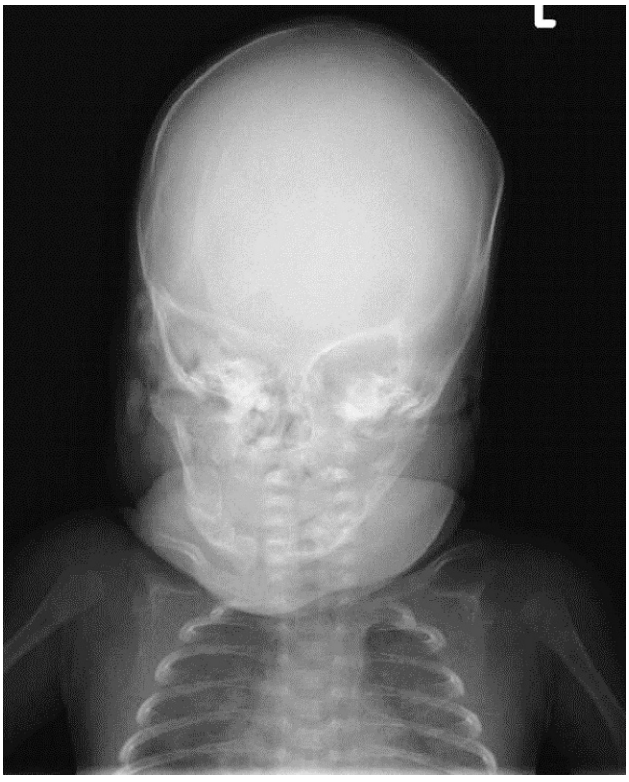

Figure 3. Case 21. Relatively thin skull vault. Again, there was no other radiologic sign of rickets.

significantly different from 7 control cases, in which sudden death at <1 year was fully explained (16.9 ± 5.2 ng/mL) and higher than 17 in-hospital death control cases (11.9 ± 4.4 ng/mL). This is not surprising, because the in-hospital cases are often chronically ill prior to death. This study concluded that VDD does not contribute to the underlying pathophysiology of SIDS.

There were 25 cases of unexplained death in our cohort, including 19 SIDS, 4 SUDC and 2 sudden unexpected death in epilepsy. Whether or not VDD is linked to SIDS remains unknown. Sudden infant death syndrome has many known risk factors, including male sex, young mother, maternal smoking during or after pregnancy, low socioeconomic status, prematurity, low birth weight, and prone sleeping position. Some of these factors are also associated with VDD, such as low socioeconomic status and prematurity. Therefore, the role of VDD in SIDS, if any, is difficult to prove without accounting for these confounding factors. However, there are several potential mechanisms by which VDD might contribute to SIDS.

Ladhani and colleaguesl [28] have reported that 29 of 65 children with VDD (45%) presented with symptoms of hypocalcaemia, including convulsions and apnea, with no radiologic evidence of rickets. Another study [9] also showed that 12% of the patients with VDD presented with a fit secondary to hypocalcemia. Therefore, it is plausible that VDD with secondary hypocalcemia could cause SIDS as a result of a seizure, apnea, or laryngospasm. Unfortunately, calcium and parathyroid hormone levels are not routinely measured at postmortem.

It has been shown that vitamin D can affect the viability, integrity, connectivity, and function of both neuronal and non-neuronal cells in the developing brain [29,30]. Therefore, it can be speculated that VDD may contribute to SIDS through subtle abnormalities in brain structure or function that cannot be detected at postmortem.

The histologic features of rickets reflect the failure of the cartilage to mineralize and undergo resorption, resulting in disarray and expansion in thickness and lateral width of the growth plate (cupping of the costochondral junction) [17]. In addition, the columnar arrangement of the distal chondrocytes is lost, and islands of unmineralized cartilage surrounded by osteoid occupy the metaphysis [18]. Other histologic features that characterize rickets include inadequate removal of the cartilage and invasion of the growth plate by blood vessels, irregular and thickened trabeculae due to an excess of osteoid (''osteoid seams''), and a core of woven bone (bone mixed with partially calcified cartilage) surrounded by lamellar bone and a rim of osteoblasts [17,18]. Although none of our cases depicted all the above described features that characterize rickets, 1 or more abnormality was seen in 69%. These findings suggest that vitamin D levels need to fall below a certain threshold before bone abnormalities become apparent on histology.

Our finding of a higher incidence of bone abnormalities on histology compared with radiology (69% versus 19%) is not unexpected. Bone calcium content needs to reduce by at least 30% before reduced density is appreciated by radiography [31]. Moreover, some specific histologic features of rickets, such as thickening of the cartilaginous growth plate and presence of penetrating vessels, cannot be detected on radiographic imaging. It is likely that the abnormal trabeculae seen under the microscope reflect as reduced bone density on radiographs. Interestingly, 2 cases with adequate vitamin D levels in our cohort (cases 6 and 10) showed abnormal features. Case 6 had widening of the metaphysis, and case 10 had thickening of the growth plate, penetrating vessels into the cartilaginous plate, and abnormal trabeculae. The reviewed radiology on this latter case was also abnormal, showing reduced bone density and changes suggestive of rickets. It is possible that this patient had some type of vitamin D–resistant rickets.

In conclusion, we have shown that a significant proportion of infants and children who died suddenly and unexpectedly had inadequate levels of vitamin D. Our cohort included 25 cases in which the cause of death remained unexplained after a thorough postmortem examination. We had insufficient data to confirm or exclude an association between VDD and increased risk of infection. The histology of the ribs demonstrated abnormal features in a high proportion of infants and children with inadequate levels of vitamin D. The radiology identified abnormalities in less than one third of the cases in which the histology was abnormal.

The results of this service evaluation are limited in that it is an observation, and therefore causality should not be inferred. Further multicenter studies are needed to confirm our findings and explore possible associations between VDD and other known risk factors for SIDS. If confirmed, randomized clinical trials may be useful to determine whether vitamin D supplementation could have any potential benefit in reducing the incidence of SIDS and SUDC.

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LETTER TO THE EDITOR

Limitations of Radiology in Rickets

To the Editor,

I congratulate Dr. Cohen and colleagues for reporting on the histopathologic evidence of rickets in deceased infants and children [1]. I would like the opportunity to highlight some of the relevant findings from their study's data.

The histologic features of rickets in deceased infants in the 1st year of life were alarmingly high (13 of 15, or 86.7%), peaking in the 1st 4 months of life. This is not surprising in light of recent reports of excessive rates of vitamin D deficiency in mothers and their offspring at birth [2]. Their findings are also supportive of recent reports describing unsuspected rickets mimicking child abuse in early infancy, as published in peer-reviewed literature [3,4] and the British press [5]. It is interesting to note that Cohen and colleagues reported no histologic rickets in the 7 subjects beyond 1-year of age. It may be reasonable to conclude from this small study that the subclinical, early infantile form of disease may actually predominate over classical rickets, which usually presents in the 2nd year of life, a conclusion that, until now, would have been considered highly controversial.

Moreover, no cases of rickets had been correctly identified by the original radiologists interpreting the skeletal images at the time of illness or demise. Even when retrospectively assessing skeletal surveys for this study, 2 pediatric radiologists had a combined sensitivity for detecting rickets of only 15.4%, failing to unanimously agree on the only 2 cases they identified. It should be emphasized, therefore, that the radiologic assessment is considerably less sensitive than histopathology. It can also be concluded that normal radiographs do not dismiss the presence of histologic rickets. This has particularly important implications in the workup of infants with unexplained fractures who are being evaluated for possible child abuse.

Histologic evidence of rickets was present in 2 of 9 (22.2%) study subjects with sufficient levels of vitamin D (>75 nmol/L), the peak level as high as 115.9 nmol/L (case 10). This supports the historically recognized observation that rickets cannot be excluded by normal 25-hydroxyvitamin D levels alone. It is particularly perplexing, therefore, that 2 of the study co-authors (Offiah and Sprigg) could endorse the British Paediatric and Adolescent Bone Group's recent position statement on vitamin D deficiency, which concluded, ''In infants with unexplained fractures, unless conventional radiography and biochemistry (abnormal blood concentrations of calcium, phosphate, alkaline phosphatase, or parathyroid hormone) provide evidence of rickets, 25 hydroxyvitamin D is not implicated'' [6].

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Response to Ayoub: Letter to the Editor; Limitations of Radiology in Rickets

We are grateful to Dr Ayoub for his comments about our recent study, which addressed the histopathologic evidence of rickets in deceased infants and children [1].

Rickets is a metabolic bone disease with biochemical and histologic changes that when established has typical radiologic features. The diagnosis of rickets requires measurement of calcium, phosphate, alkaline phosphatase, and parathyroid hormone, none of which were measured in our postmortem cases. The histologic changes present in our study group were in keeping with early stages of rickets, for which radiology is obviously not sensitive enough. We do not know if the condition was fully developed in the patients with more marked changes, because no tests were performed in life and the children did not have clinical evidence of rickets.

Radiology performs well in depicting changes of well-established rickets. Our paper demonstrates that early changes of vitamin D insufficiency/deficiency are not seen on radiographs. This is not an unexpected finding, because histology examines the tissue at higher magnification (×60).

Our numbers are relatively small, and no definite conclusion can be reached as to the relationship between vitamin D levels, abnormal histopathology, and bone fragility. More research is required on the topic, as requested by the British Paediatric and Adolescent Bone Group and by the Royal College of Paediatrics and Child Health [2].

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