Continuing clinically severe vitamin D deficiency in Asians in the UK (Leicester)

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Summary: Deprivational vitamin D deficiency began to be noted in immigrant Asians in the early 1960s. Although there have been suggestions that the level of this problem may be declining, we describe a number of clinical cases seen over a consecutive 3½ year period. Musculoskeletal symptoms were the commonest though there were a variety of medical presentations requiring hospital referral. Most of the cases were Hindu vegetarians. There is likely to be significant underdiagnosis of this condition.

In spite of the extensive medical, social and political attention this condition has received, our study shows that vitamin D deficiency continues to persist in certain Asians in a clinically florid fashion. An effective preventative policy is long overdue.

Introduction

Vitamin D deficiency was noted in Asian immigrants in the UK in the early 1960s¹ but the current level of this problem remains unclear. Although it has been suggested that the incidence of this condition may be declining,^{2,3} others have reported a persistence^{4,5} and a recent study showed 6% of patients screened in outpatients had evidence of histological osteomalacia.⁶ Leicester has a relatively large Asian population and there have been no previous published reports of any clinical cases of vitamin D deficiency from this city. In a recently set up metabolic bone disease clinic, we have seen a number of clinically florid cases of deprivational vitamin D deficiency in Asians. We describe some of these cases seen recently.

Patients and methods

Patients

Patients described are those who presented medically over a consecutive 3½ year period. They were referred through a metabolic bone disease clinic that has links with a rheumatology clinic. Some patients presented through a nephrology clinic and are also described. Leicestershire has a total population of 865,133, of which 8.9% are Asians, and Leicester City has a domestic popula-

tion of 266,473, of which 23.7% are Asians (Population Census 1991). The vast majority of the Asians in Leicestershire are of Indian origin, and a much smaller number from Pakistan and Bangladesh. There is a further smaller proportion of Chinese and other Asians.

Methods

The routine biochemistry was analysed on either a SMAC I or SMAC II analyser using standard methodology. The 25-hydroxyvitamin D [25(OH) VitD] levels were measured by a competitive protein-binding assay kindly performed by the SAS Laboratory, Middlesex Hospital (now University College, Middlesex Hospital Medical School) in London. Bone biopsies were done after written consent, using a Nicholson trephine from the superior iliac crest. The biopsy was taken under sedation and with local anaesthesia. Undecalcified sections were stained for osteoid using the Trip and McKay method.⁷

Results

The clinical, biochemical, radiological and bone biopsy results of individual patients are shown in Table I. The age distribution and summary of the clinical presentations are shown in Table II. The distribution of biochemical results are shown in Table II and plotted on Figure 1.

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Table 1 Clinical, biochemical and bone biopsy from 26 patients

Patient no.	Age (years)	Sex	Clinical features	Biochemistry					X-rays	Bone biopsy
				Adjusted calcium (mmol/l) (RR 2.10–2.60)	Albumin (g/l) (RR 35–53)	PO ₄ (mmol/l) (RR 0.8–1.40)	Alkaline phosphatase (IU/l) (RR adult 30–130, children 30–330)	25 (OH) VitD (ng/ml) (RR 3–30)		
1	40	M	Pain in forefoot, ? polyarthritits	2.0	49	0.88	164	–	NAD	–
2	13	M	Hypocalcaemic fits	1.77	45	1.71	503	<1.0	NAD	–
3	2 months	M	Hypocalcaemic fits	1.08	39	–	1,088	<1.0	+	–
4	57	F	Back pain	2.41	42	1.32	330	–	+	?
5	43	F	Shoulder and hip pain, difficulty in walking	2.19	36	0.59	119	–	–	+
6	43	F	Hypocalcaemic, cardiac failure	1.92	41	1.72	–	3.4	–	+
7	22	F	General aches	2.02	41	1.01	160	<1.0	–	–
8	30	F	Hip pain	2.18	40	0.26	149	–	–	+
9	59	M	Back pain	2.18	48	1.02	274	3.4	?	+
10	22	F	Weakness, numbness, tingling	1.78	47	0.90	274	<1.0	?	+
11	21	F	Hypocalcaemic fits in pregnancy, hypoparathyroidism (?)	1.49	30	1.25	83	1.3	–	–
12	48	F	Lower limb pain	2.10	43	0.77	239	7.6	+	–
13	58	F	Rib pain	2.16	45	0.81	332	<1.0	?	+
14	31	F	Pains in shoulders	1.92	40	0.63	150	<1.0	–	–
15	1	F	Failure to thrive	2.12	41	0.78	1,943	2.0	+	–
16	45	F	Weakness	1.63	44	0.87	118	<1.0	–	–
17	61	M	Weakness, difficulty in walking, joint pain	2.07	44	0.91	628	<1.0	+	–
18	32	F	Weakness, difficulty in walking	2.10	46	0.89	261	–	–	+
19	37	F	Back pain, knee pain	2.38	40	0.79	172	1.1	–	–
20	35	F	Weight loss, weakness	1.57	41	1.08	196	<1.0	–	–
21	18	F	Weakness, difficulty in walking	2.15	39	0.68	697	2.52	+	–
22	40	F	Pain/stiffness walking	2.08	40	0.57	550	7.03	–	+
23	25	F	Pain/stiffness walking	2.27	41	0.76	1,067	1.52	–	+
24	52	F	Weakness, renal failure	1.85	32	1.11	369	2.03	–	–
25	51	F	Weakness, parathyroid adenoma	2.34	40	1.10	181	3.0	–	–
26	33	F	Post-renal transplant, pain/stiffness walking	1.77	41	0.83	211	<1.0	+	–

+ = abnormal result; ? = equivocal result; – = investigation not undertaken; NAD = no abnormality detected on investigation; RR = reference range.

Table II Age distribution, summary of the clinical presentations and distribution of biochemical results for Asian patients with vitamin D deficiency

Patients	Age (years)			Clinical features	No. of patients	Biochemistry			
	15–20	21–40	41–60			Adjusted calcium (mmol/l)	Phosphate (mmol/l)	Alkaline phosphate (IU/l)	25(OH) VitD (ng/ml)
Adults				Difficulty in walking	7	Reference range	0.8–1.40	40–130	3.0–30
Males				Waddling gait	4	Mean	0.93	406.32	1.67
Females		1	2	Weakness	4	s.d.	0.33	419.9	2.2
		12	8	Joint pain	3				
Children				Back pain	3	Confidence interval			
	0–1	1–5	6–15	Bone pain	3	95%	0.79–1.06	90–1,233	0.64–2.7
Males	1	–	1	Hypocalcaemic fits	3	<i>n</i>	25	25	21
Females	1	–	–	Hypocalcaemic		1.86–2.11			
				Hypocalcaemia	2	26			
				parasthesiae	2				
				Cardiac failure	1				
				Failure to thrive	1				

Bone biopsy

Three patients refused a biopsy, one patient presented late in pregnancy and in two patients the biopsy was unsuitable for histomorphometry. Biopsy was not done on the three children; two of these had radiological evidence of rickets, and in the third, case no. 2, X-ray changes were inconclusive but he had characteristic biochemical changes of vitamin D deficiency. An osteoid volume of greater than the reference range of the age and sex of the patient⁸ was taken as indicating the presence of definite histological osteomalacia. One patient (case no. 4) had an osteoid volume at the extreme upper end for her age.

Clinical chemistry

Total serum calcium was adjusted for variation in albumin by $0.025 \text{ mmol} \times (40 - \text{albumin g/l})$. Fourteen patients had hypocalcaemia, nine patients had hypophosphataemia. A raised serum alkaline phosphatase was present in 19 adults ($> 130 \text{ IU/l}$) and in the three children ($> 330 \text{ IU/l}$). There was no clinical and biochemical evidence of liver disease in any patient indicating that the raised serum alkaline phosphatase was very likely of skeletal origin. Serum 25(OH)VitD was undetectably low in 10 patients. Two patients (case nos 12 and 22) who had 25(OH)VitD values well within the reference range had recently started vitamin D supplements before blood samples were taken. All the abnormal biochemical values had normalized following treatment.

X-rays

Two children had typical appearances of rickets on wrist X-rays. Seven adults had characteristic looser's zones either in the pelvis or in the femora. In three adults, there was some uncertainty about the presence of looser's zones.

Patients

The diagnosis of deprivational vitamin D deficiency was established on clinical and investigative findings, and response to therapy. From a total of ten patients not having radiological and/or histological evidence of vitamin D deficiency, eight patients (case nos 1, 2, 7, 14, 16, 19, 24, 25), amongst other biochemical abnormalities, had a raised serum alkaline phosphatase. A raised serum alkaline phosphatase in this setting has previously been shown to be indicative of histological osteomalacia,⁹ and radiological rickets.¹⁰ A recent study describing osteomalacia patients categorized them into five (I–V) groups.⁵ Those in groups IV and V had evidence of histological osteomalacia.

Figure 1 Biochemical results of Asian patients with vitamin D deficiency. For (a) adjusted total calcium; (b) phosphate; (c) alkaline phosphatase; and (d) 25(OH)VitD. The boxed area shows the reference range; ○ = patients with histological osteomalacia; ● = other patients.

Only these subgroups also had a raised serum alkaline phosphatase. It is highly likely therefore that our patients with a raised serum alkaline phosphatase would have had histological or radiological evidence of vitamin D deficiency, had these investigations been possible. Of the other two patients in this group, case no. 11 had hypocalcaemia and very low 25(OH)VitD levels, and was a Hindu vegetarian. In spite of the hypocalcaemia her serum parathyroid hormone level (PTH) was low, 2.1 pmol/l (0.8–5.4 pmol/l), using an 'intact' PTH assay. We feel she also had hypoparathyroidism in addition to vitamin D deficiency but she was lost to follow-up. Case no. 16 had hypocalcaemia and undetectable 25(OH)VitD levels.

Most patients presented with musculoskeletal symptoms and, because of the vague nature of the complaints, in some instances the diagnosis was unsuspected. Many of the patients with walking difficulties had noted symptoms for 'years'. One case (no. 23) in particular had noted great difficulty in walking for 3 years prior to diagnosis, since the birth of her only child. Four cases had typical waddling gait on presentation. Three patients presented with hypocalcaemic fits, all requiring intravenous therapy to control their fitting. Once hypocalcaemia has been diagnosed, intravenous calcium gluconate was necessary in all three for control of hypocalcaemia. One patient (case no. 11) who presented with fits late in pregnancy probably also had underlying hypoparathyroidism. In addition to oral calciferol and calcium supplements, she required 1 α cholecalciferol to normalize her serum calcium. Case no. 6 presented with cardiac failure which was due to hypocalcaemia from vitamin D deficiency and she has been described in detail elsewhere.¹¹

Another patient (case no. 20) had been investigated for infertility for over 2 years and within 3 months of treatment conceived and subsequently delivered a healthy child. Twenty-three of the patients described were Hindu or from Hindu families who were vegetarians. Other nutritional deficiencies which required treatment included vitamin B₁₂ deficiency in four and iron deficiency in seven patients. Four patients had been treated from tuberculosis in the recent past.

These are all patients whose presenting clinical problems proved essentially to be due to deprivational vitamin D deficiency. All patients described have had complete clinical and biochemical resolution following treatment with standard regimes of oral calciferol and calcium supplements.

Discussion

Over 30 years ago, Glasgow¹ was one of the first cities to draw attention to the problem of deprivational vitamin D deficiency in the Asians in the UK. Since then there have been reports from other cities in the UK including London,¹² Birmingham¹³ and Manchester.¹⁴ Surprisingly, there have been no previous published reports of any clinical cases from Leicester, a city which is well known to have had a large proportion of Asians from the 1960s onwards following migration both from the Indian subcontinent and East Africa.

The earliest clinical cases to be described in detail were in 1962 from a Pakistani family in Glasgow following the presentation of a 14 year old girl with active rickets.¹ In the same study, a survey of immigrant schoolchildren and their families showed 35 of the 74 people screened had evidence

of vitamin D deficiency.¹ A resurvey by the same group 10 years later in 1971¹⁵ showed 24% of the 115 people screened had vitamin D deficiency. Over the three years prior to this survey, 21 cases of rickets had presented to Glasgow hospitals.

Earlier reports of this problem from Glasgow were in the Pakistani (Muslim)^{1,15} immigrants but more recently it has been reported in the Hindu vegetarians.^{5,16} The majority of our patients were Indian Hindu vegetarians. The largest proportion of Asians in Leicester are Hindu Gujaratis and this may have biased our patient type. Vitamin D deficiency in Asians has been described in different age groups: neonatal,¹⁷ infantile,¹⁸ adolescent⁴ and adults.^{1,5} Most of our patients were women, many of childbearing age. Our patient type may be a biased representation of the problem from the nature of the adult clinic. How common the problem is locally in other age groups, especially children, remains unclear.

Recently, a study that screened for vitamin D deficiency in Asians referred to a General Medical Clinic, classified 6% (11 cases) as having had severe osteomalacia associated with severe thigh pain, gait change and difficulty in rising.⁵ Surprisingly, none of these patients had been referred with a possible diagnosis of metabolic bone disease. From the nature of the study, all of the clinical symptoms from this study were attributed to the musculoskeletal system.

In our cases musculoskeletal symptoms and signs were also the commonest but on referral many of these features, although often severe, were not considered to be significant. Since musculoskeletal symptoms may be vague and non-specific and signs equivocal or minimal, although often not initially considered, many patients turn out to have severe vitamin D deficiency. We have also seen a variety of other medical presentations mainly associated with hypocalcaemia. It has recently been emphasized again that because of the non-specificity of presentation, the diagnosis of osteomalacia may easily be missed in the UK.¹⁹

Many of the presenting clinical problems can be related to the disturbed classical calcitropic effects of vitamin D. However, there is increasing recognition that vitamin D has a more widespread role in non-classical target tissues including its role in immune modulation.²⁰ The altered immune response in vitamin D deficiency may possibly be linked to the predisposition Asians have for infections, especially tuberculosis;^{21,22} excess morbidity from these conditions having been confirmed by a recent study from this city.²³ Four of our cases had been treated for tuberculosis. Other 'nutritional' deficiencies may also be common as in some of our patients. Although nutritional B₁₂ deficiency is also well recognized in this group, the incidence of true pernicious anaemia is higher than expected.²⁴

The risk factors associated with the development of vitamin D deficiency in Asians have been studied by the Glasgow group.^{25,26} The development of rickets was associated with higher intake of chapatti, lower daylight exposure and lower intake of meat.²⁵ Prevalence of rickets had a North-South gradient (Glasgow, Bradford, Coventry).²⁵ The findings in osteomalacias were slightly different; levels of daylight exposure and high extraction of wheat cereal discriminated poorly and the degree of vegetarianism was a strong risk factor.²⁶ The apparent difference between risk factors of osteomalacia and rickets were suggested to be due to the difference in growth requirements.²⁶ When exposure to UV radiation is limited, dietary factors may be important in the development of this condition.²⁶ It has been suggested that a low calcium and high cereal diet may enhance the inactivation of vitamin D from a state of secondary hyperparathyroidism.²

Awareness of this problem led to the suggestion of some preventive policies; daily or annual supplements²⁷ and fortification of chapatti flour²⁸ with vitamin D have been suggested. A Department of Health Working Party rejected the idea of fortification of milk, butter and flour, including chapatti flour, with vitamin D, although fortification of margarine was recommended.²⁹ Following the setting up of preventive policies, apart from in Glasgow, there have been few follow-up studies.³⁰ Glasgow appears to have reported some success in the control of this problem in children³⁰ but had a disappointing outcome in adults.³¹

From the 1960s onwards, Leicester Health Authority was aware of the potential medical problems of an influx of immigrants. There are conflicting anecdotal but not fully medically published reports of clinical vitamin D deficiency locally. One study did show a slight excess of 'endocrine nutritional and metabolic disease' [ICD-(240-279)] in Asians but vitamin D was not looked at specifically.²³ Following a dietary survey in a school with a high number of immigrants,³² the local health authority adopted a policy of sending a letter to all new pupils of secondary schools between 1975 and 1980. Leicester was one of the three national centres chosen for the 'stop the rickets' campaign in 1981 but did not adopt a policy of issuing free vitamin D supplements. There is a local policy to prescribe calcium and vitamin D tablets routinely during pregnancy. Although two of our cases (case nos 7 and 11) were related to lack of compliance during pregnancy, many of our cases presented outside this category. Such people may not be aware of the importance of vitamin D.

Should a further preventative policy be considered in Leicester? Although, recently it has been suggested that with dietary adaptation the problem may eventually disappear,⁵ we believe this may take

some time, possibly decades, and in the interim will not only cause considerable range and severity of morbidity but also be financially costly. The need for proper prevalence studies has been emphasized.³³ Awareness of the problem with some form of vitamin D supplementation would seem a possible way. However, in view of the variable success,^{30,31,34} a very carefully planned policy would be needed.

Deprivational rickets has been known for centuries in Europe and reached a high prevalence in Victorian England.³⁵ It is surprising that we still see simple 'nutritional' vitamin D deficiency within modern developed society albeit in a socially and

culturally distinct subgroup. The observation that such overt clinical cases are presenting to hospital is not only surprising but a cause for concern. Further, we have only described patients who have presented to a selected specialty but we know of other cases who have presented through a variety of other general medical specialties. In spite of the extensive medical, social and political attention vitamin D deficiency in Asians has received, our study showing overt clinical cases has emphasized that at least in some parts of the UK this continues to be a significant clinical problem, adding to the liable economic burden of the Health Service. An effective preventive policy is long overdue.

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