

Congenital Rickets Presenting with Hypocalcaemic Seizures

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ABSTRACT

At Ataturk University Hospital, eight infants who presented with hypocalcaemic seizures were subsequently found to have rickets. Their mothers had osteomalacia. Neither mothers nor infants received vitamin D supplementation. Maternal vitamin D deficiency and non-supplementation in the infants were causes of rickets in these patients. It is recommended that neonatal hypocalcaemia may be due to maternal vitamin D deficiency and all unsupplemented vitamin D infants presenting with seizures should be investigated for rickets.

Raquitismo Congénito Acompañado de Ataques Hipocalcémicos

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RESUMEN

En el Hospital Universitario Ataturk, se halló que ocho infantes que se presentaron con ataques hipocalcémicos, padecían también de raquitismo. Sus madres tenían osteomalacia. Ni madres ni infantes recibieron suplementación de vitamina D. La deficiencia materna de vitamina D y la falta de su suplementación en los infantes fueron la causa de raquitismos en estos pacientes. Se sugiere que la hipocalcemia neonatal pueda ser consecuencia de la deficiencia materna de vitamina D, y se recomienda que todos los infantes sin suplemento de vitamina D que se presenten con ataques, sean investigados en relación con el raquitismo.

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INTRODUCTION

Cholecalciferol or vitamin D₃ is generally considered to be a prohormone synthesized in the skin after exposure to ultraviolet radiation; 7-dehydrocholesterol is converted to pre-cholecalciferol and through thermal isomerization to cholecalciferol. Vitamin D₂ or ergocalciferol is produced by ultraviolet radiation of the plant sterol ergosterol. Vitamin D₂ and D₃ are virtually equipotent in humans and can be included under the general name vitamin D (1).

In adults, the disorder is known as osteomalacia. Rickets is a disorder that results from inadequate mineral deposition in children's bones. On the other hand, it may be referred to as calcium deficiency which is caused by a deficiency of vitamin D (actually a steroid hormone). Vitamin D regulates blood levels of calcium and phosphorus to support proper mineralization of bone. Dietary calcium is not very well absorbed by the body, and the most important function of vitamin D is to facilitate intestinal absorption of calcium (2). Although clinical features may point to rickets

or osteomalacia, the diagnosis depends on laboratory studies. The chemical picture can vary with different stages of disease. In infants with vitamin D deficiency, serum calcium may be low and the serum phosphorus concentration may be normal initially; as secondary hyperparathyroidism however, calcium concentrations usually return to the low-normal range and serum phosphorus levels fall further. In advanced stages, the serum calcium concentration may fall again. This fall has been attributed to the inability of secondary hyperparathyroidism to maintain the secondary calcium level when the bone surface is covered by osteoid and is resistant to attack by osteoclasts (3). In adults, the characteristic picture is a low-normal or slightly decreased serum calcium level, a decreased urinary calcium level and a low serum phosphate level. Increased alkaline phosphatase level reflect the activity of osteoblasts which form unmineralized matrix. Parathyroid hormone levels may be markedly increased. The key diagnostic test in vitamin D deficiency is demonstration of a decreased serum 25-hydroxyvitamin D value (3). Maternal vitamin D deficiency leads to fetal then neonatal vitamin D deficiency. In neonates, physical findings may not be obvious or appreciated by even the astute clinician during the early stages of vitamin D deficiency rickets. In advanced stages, rickets may present with hypocalcaemic seizure. In one study, the primary presenting problem was seizure in 5 of

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63 older infants (4). Congenital rickets results when maternal vitamin D and calcium is low. Neonatal vitamin D deficiency and congenital rickets are extremely rare and are seen only when there has been advanced maternal osteomalacia and vitamin D deficiency. Vitamin D status at birth is directly related to maternal vitamin D status (5). It was shown that placental vein 25-hydroxyvitamin D and 24, 25-dihydroxyvitamin D concentrations correlated significantly with those found in the maternal circulation, implying that these two secosteroids diffuse easily across the placental barrier and that the vitamin D pool of the fetus depended entirely on that of the mother (6). Vitamin D deficiency or congenital rickets caused maternal D deficiency similar to the vitamin D deficient rickets noted in older children (5).

Vitamin D deficiency continues to be a problem in developing countries. In early infancy, vitamin D status depends mainly on the store of vitamin D gained across the placenta during intrauterine life. So, maternal vitamin D deficiency can adversely affect the offspring in terms of delayed growth or bone ossification, abnormal enamel formation and especially alterations in calcium metabolism during the neonatal period (1). Laryngospasm with cyanosis and apnoeic episodes, poor feeding, vomiting and lethargy are nonspecific associated manifestations (7). However, convulsions are the most characteristic manifestation of hypocalcaemia.

There are few reports of maternal hypovitaminosis D and rickets in breast-fed infants during early infancy. Recently, the authors saw many young infants who presented with hypocalcaemic seizures and were found to have congenital vitamin D deficiency rickets. We report eight patients with congenital rickets presenting with hypocalcaemic seizure.

SUBJECTS AND METHODS

In this study, eight patients with congenital rickets were evaluated. Diagnosis of congenital rickets had been made according to clinical, biochemical and radiological evidence after hypocalcaemic seizure in all infants. A detailed history was obtained from mothers: maternal age, number of pregnancies, maternal economic and educational status and wearing of traditional attire (covered and uncovered). Mothers who graduated from high school or university were grouped as the educated. Covered meant covering the hair and sometimes part of the face with a scarf and wearing clothes that completely covered the arms and legs (8). Economic status of the cases were determined and divided into three groups with the income ranges (low, moderate and high economic level). None of the mothers had sufficient antenatal care and vitamin D supplementation during pregnancy. Age, nutrition and vitamin D supplementation for babies were examined. Calcium (range: 2.12–2.62 mmol/L), phosphorus (range: 1.44–1.76 mmol/L) and alkaline phosphatase levels (range: 105–210 IU for baby, 30–90 IU for mother) were measured by spectrophotometric method, intact parathyroid hormone (range: 45–270 micromol/L) and 25-hydroxyvitamin D (25-OH vitamin D) (range: 23.2–92.8 (micromol/L) levels were determined by chemiluminescence and radioimmunoassay methods, respectively.

RESULTS

None of the mothers had chronic renal failure, malabsorption, liver diseases and was on anticonvulsant therapy. Each woman delivered a single infant. The demographic and biochemical properties of mothers are shown in Table 1. None of the mothers and babies had previously received

Table 1: Properties of mothers

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (yr)	21	19	27	31	28	26	18	28
Number of pregnancies	1	1	3	4	4	3	1	3
Time after last pregnancy (y)	–	–	2.5	3	7	1.5	–	4
Economic class	MEC**	LEC*	LEC*	LEC*	LEC*	LEC*	LEC*	MEC**
Dress	Covered	Covered	Covered	Covered	Covered	Covered	Covered	Uncovered
Education	Unedu.	Unedu.	Unedu.	Unedu.	Edu.	Unedu.	Unedu.	Edu.
Calcium (mmol/L)	2.37	2.22	2.4	2.27	2.1	2.22	2.37	2.27
Phosphorus (mmol/L)	1.29	1.35	1.45	1.51	1.29	1.22	1.13	1.25
Alkaline phosphatase (IU/L)	227	317	286	304	347	199	461	251
Parathyroid hormone (micromol/L)	356	405	352	483	517	585	735	491
25-OH-vitamin D (micromol/L)	6.9	–	16.2	–	18.6	13.9	11.6	11.6

*LEC: lower economic class, **MEC: moderate economic class

vitamin D supplementation. Although 25-hydroxyvitamin D levels were not measured because of economic constraints in two mothers, all had osteomalacia due to vitamin D deficiency (Table 1). Wearing of traditional attire (covered) was another contributing important factor.

All patients were fed breast-milk without formula supplements. There was no nutrition with cow's milk causing a high phosphate load. The serum magnesium levels of all babies were in the normal range. Data from the babies are shown in Table 2. The sutures were widely separated, the

deficiency (12). In the present study, serum concentrations of 25-hydroxyvitamin D were determined before and after a three-week rehabilitation treatment at 1000 m above sea level and found to be increased (12). Also, it was known that inadequate exposure to ultraviolet B radiation prevented the conversion of the prohormone to the hormonal form of vitamin D at high latitudes (13). Our results demonstrated that, despite the moderate latitudes (sunny climate) and high altitude (1850 m above sea level), vitamin D deficiency was an important problem for reproductive women in Turkey. In-

Table 2: Properties of babies

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (day)	60	60	60	50	44	35	40	45
Sex	Male	Male	Male	Female	Male	Male	Male	Male
Weight (g)	3950	4700	5000	3900	4450	4000	4800	5300
(percentile)	10–25	25–50	50	3 ↓	10–25	25	3–10	25–50
Season at birth	Summer	Fall	Fall	Fall	Winter	Fall	summer	Winter
Type of seizure	GTC*	GTC*	GTC*	GTC*	GTC*	GTC*	PTC**	GTC*
Rachitic rosary	+	+	+	+	+	+	+	+
Soft skull bones	+	+	+	+	+	+	+	+
Skeletal sign at radiography	+	+	+	+	+	+	+	+
Calcium (mmol/L)	1.4	1.65	1.62	1.57	1.72	1.27	1.65	1.9
Phosphorus (mmol/L)	1.16	1.19	1.19	0.93	0.77	1.32	1.35	1.09
Alkaline phosphatase (IU/L)	1492	1722	1175	377	1607	1035	822	1642
Parathyroid hormone (micromol/L)	892	3667	828	843	1113	675	675	1050
25-OH-vitamin D (micromol/L)	20.9	6.9	13.9	18.6	11.6	11.6	13.9	9.3

* GTC: generalized tonic clonic seizure, ** PTC: partially tonic clonic seizure

fontanelles large and the skull bones soft; and laboratory studies demonstrated decreased serum calcium and phosphorus, elevated serum alkaline phosphatase and parathyroid hormone and decreased hydroxyvitamin D in all patients. Radiography revealed irregular fraying of the provisional zones of calcification and slight widening of the metaphyses in the distal femora, radii and ulnae.

DISCUSSION

In the patients in this review, hypocalcaemia and hypocalcaemic seizure were associated with a deficiency of vitamin D. It is known that affected newborns have very low calcium levels and may present with seizures or tetany in early infancy (9). In another study, Zeghoud *et al* (10) found that 24% of the neonates born to mothers who did not received vitamin D supplements were vitamin D-deficient without physical signs of such. Our finding supported the suggestion made by Purvis *et al* (11) that maternal vitamin D deficiency was a cause of hypocalcaemia in the neonate. Biochemical survey for osteomalacia should be performed routinely in the antenatal care of Asian women.

The results of one study suggested that a sojourn at high altitude in early spring was liable to reduce vitamin D

adequate vitamin D intake, complete covering garments with low economic level may be predictors of hypo-vitaminosis D. The importance of the dress code in the occurrence of vitamin D deficiency was emphasized in a prospective case-control study in Kuwaiti, another sunny country. This showed significantly lower serum 25-hydroxyvitamin D concentrations in veiled *versus* unveiled women (14). Rickets and osteomalacia, however, are the clinically overt outcomes of vitamin D deficiency which represent only the tip of the iceberg. The real problem may be undiagnosed vitamin D deficiency in reproductive women and their babies. Prophylactic vitamin D administration to pregnant and nursing mothers is necessary to prevent vitamin D deficiency in Turkey.

Under normal circumstances, circulating concentrations of 25-hydroxyvitamin D can be regarded as a good index of vitamin D status (1). In humans, endogenous synthesis from sunshine exposure is an important source of vitamin D (1). During the spring and summer months, mothers and infants are generally exposed to sufficient sunlight to prevent vitamin D deficiency, but during the colder winter months they spend less time outdoors and are bundled in several layers of protective clothing (9). Infants born in

winter or early spring to mothers of low social class with subclinical vitamin D intake are at increased risk (7). So, large seasonal variations in serum 25-hydroxyvitamin D concentrations can be observed in infants. Six of the babies in this study were born at summer and fall.

Because maternal vitamin D deficiency is often clinically silent, routine determination of calcium and phosphorus in maternal blood is in order if no obvious cause for the hypocalcaemia is present. Although the vitamin D levels were not measured in all mothers because of economic problems, serum PTH levels in them were high. Increased serum immunoreactive PTH may be a highly sensitive indicator of occult osteomalacia in this case.

Maternal vitamin D deficiency and insufficient supplementation of infants were main causes of rickets in our patients.

Treatment of the seizures was accomplished by slow intravenous administration of 10% calcium gluconate (2 mL/kg) while monitoring the cardiac rate. Maintenance oral treatment was performed with a dose of 75 mg/kg/day of elemental calcium. Vitamin D supplementation was made by 300 000 U cholecalciferol intramuscularly. All patients responded to vitamin D and calcium supplements at follow-up. All showed complete healing of the rickets biochemically within two months. The diagnosis of rickets was confirmed by clinical findings.

Rickets, in addition to being a nutritional disorder, is a cultural disease. For adults with osteomalacia, it is important to consider not only the patient's diet but their cultural background as well.

Maternal vitamin D deficiency can adversely affect the offspring in terms of delayed growth or bone ossification, abnormal enamel formation and alterations in calcium metabolism during the neonatal period (1). It is also known that the resulting low levels of serum vitamin D in the pregnant woman disrupt calcium homeostasis leading to intrauterine growth retardation, premature labour and hypertension (13). All are important perinatal risk factors. In this paper, a further example of congenital rickets is described in a baby whose mother had biochemical evidence of osteomalacia, and presents new evidence that neonatal hypocalcaemia may be due to maternal vitamin D deficiency. Biochemical screening of pregnant Asian women for vitamin D deficiency or osteopenia should be a routine part of antenatal care, and

vitamin D supplementation must be made. Further, infants who are not receiving vitamin D supplementation and present with seizures should undergo biochemical and other investigations for rickets. Also, this article suggests that hypovitaminosis D is a public health problem in Turkey and further studies are urgently needed to assess the prevalence of osteomalacia in Asian women and rickets in their infants. Therefore, the very important relationship between maternal and neonatal vitamin D status, rickets and calcium disturbances must be re-emphasized as an important treatable cause of infantile seizures.

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