Vitamin D Deficiency Rickets in Infants Presenting with Hypocalcaemic Convulsions

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ABSTRACT

Aim: *Hypocalcaemia evaluation of the clinical, biochemical and radiological features of 91 infants with rickets who presented as hypocalcaemic convulsions.*

Subjects and Methods: *Ninety-one hypocalcaemic infants who were brought to hospital with convulsion and diag-nosed with rickets related to vitamin D deficiency according to their clinical, biochemical and radio-logical features were retrospectively reviewed.*

Results: *Mean values of the laboratory data were as follows: calcium 5.55 ± 0.79 mg/dL, phosphorus 4.77 ± 1.66 mg/dL, alkaline phosphatase 1525.5 ± 925.4 U/L and parathormone 256.8 ± 158.3 pg/mL. Serum 25-OH vitamin D levels were below normal (< 20 ng/mL) in 37 infants.*

Conclusion: *Vitamin D deficiency should be considered in infants presenting with hypocalcaemia. To avoid complications such as convulsions, clinicians should give vitamin D supplementation to such infants*.

Keywords: Deficiency, hypocalcamic convulsion, infancy, vitamin D

Raquitismo por Deficiencia de Vitamina D en Lactantes que Presentan Convulsiones por Hipocalcemia

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RESUMEN

Objetivo: *Evaluación hipocalcémica de los aspectos clínicos, bioquímicos y radiológicos de 91 lactantes con raquitismo, que presentaron convulsiones por hipocalcemia.*

Pacientes y métodos: *Noventa y un lactantes hipocalcémicos llevados al hospital con convulsiones y a quienes se les diagnosticó raquitismo asociado a la deficiencia de vitamina D de acuerdo con sus características, bioquímicas y radiológicas, fueron revisados retrospectivamente.*

Resultados: *Los valores medios de los datos de laboratorio fueron los siguientes: calcio 5.55 ± 0.79 mg/dL, fósforo 4.77 ± 1.66 mg/dL, fosfatasa alcalina 1525.5 ± 925.4 U/L, y paratohormona 256.8 ± 158.3 pg/mL. Los niveles séricos de la vitamina 25 (OH) D estuvieron por debajo de lo normal en 37 lactantes (< 20 ng/mL).*

Conclusión: *La deficiencia de vitamina D debe considerarse en los infantes que se presentan con hipocalcemia. A fin de evitar complicaciones tales como convulsiones, se les debe dar suplementos de vitamina D.*

Palabras claves: Deficiencia, convulsión hipocalcémica, infancia, vitamina D

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INTRODUCTION

Rickets usually occurs as a result of vitamin D deficiency. Less often, dietary deficiency of calcium (Ca) or phosphorus (P) may also cause rickets (1). Vitamin D deficiency and/or nutritional rickets are still commonly seen in developing countries. In Turkey, nutritional rickets was detected in 6% of children less than three years of age and 3.1% in those under

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the age of 15 years (2, 3). According to our clinical experiences and the literature, there is an increase in the number of infants, who are brought with convulsion to Emergency Services and diagnosed with hypocalcemic rickets in recent times (4–6).

In this article, clinical, biochemical and radiological characteristics of 91 infants with vitamin D deficiency rickets presenting with hypocalcaemic seizures have been evaluated. The aim is to emphasize the importance of seizures in infants with rickets.

SUBJECTS AND METHODS

Ninety-one hypocalcaemic infants (70 boys, 21 girls), who were brought to hospital with seizures and diagnosed with vitamin D deficiency rickets according to their clinical, biochemical and radiological characteristics, were included in the study. Clinical and laboratory findings of the cases were reviewed retrospectively.

The biochemical criteria for rickets were defined as the following: low serum 25-OH vitamin D level (≤ 20 ng/mL), increased serum alkaline phosphatase (ALP) and serum parathormone (PTH) levels or low serum Ca level (7). Rickets staging was performed according to the biochemical and radiographic findings (7). The nutritional status of children was evaluated by comparing weight measurements on a growth curve [Gomez standard] (8).

Intravenous calcium gluconate at a dose of 1 mL/kg every six hours was given to all infants. After achieving normocalcaemia, it was switched to oral calcium lactate (50–75 mg/kg of elemental calcium per day in four divided doses).

There was pneumonia in nine patients, sepsis in five, acute gastroenteritis in one, hypoglycaemia in one and hypoxic-ischaemic encephalopathy in another. All patients were treated according to the underlying cause.

RESULTS

Most of the cases (76.9%) were boys. The mean age was 6.01 ± 4.06 months (range 15 days–24 months). None of the cases had received vitamin D supplementation. Most patients were brought in the winter (41 (45%) infants) and in spring (28 (30.7%) infants). Another 12 (13.1%) and 10 (10.9%) infants were brought in autumn and summer, respectively. While 77 (84.7%) infants had clinical findings of rickets (large anterior fontanel, large hand-wrist, rachitic rosary and craniotabes), no findings were recorded in 14 (15.3%) cases. Mean laboratory values were as follows: Ca 5.55 ± 0.79 mg/dL, P 4.77 ± 1.66 mg/dL, alkaline phosphatase 1525.5 ± 925.4 U/L, and PTH 256.8 ± 158.3 pg/mL. Serum P values were variable and only 30% of all cases were below the normal range (Tables 1, 2).

Alkaline phosphatase and PTH values were high in most of the cases (94.45%, 96.52%, respectively). Serum 25-OH vitamin D levels were low in 37 patients (< 20 ng/mL). X-ray findings, which were variably consistent with rickets, were present in 36 (75%) of 48 cases. According to biochemical and radiological findings, there was grade III rickets in 32.9% of cases over 12 months of age and grade I rickets in 67.1% less than three months of age; 30.5% of the patients were found to have protein-energy malnutrition (Table 3).

Vitamin D deficiency was the main cause in all of the patients. None of the patients had received vitamin D prophylaxis during infancy and their diet consisted mainly of breast or cow's milk.

Treatments used in 79 patients with treatment-related data are as follows: 300.000 IU in 45 (49.5%), 150.000 IU in 22 (24.2%), and 1000 IU/day in 12 (13.2%) [with mild radiological findings].

None of the infants had developed convulsions after initial therapy. At examination after six weeks, hypercalcaemia was diagnosed in one of 21 patients (19.3 mg/dL) receiving 1000 IU/day vitamin D; in this patient, serum PTH level was suppressed (4.7 pg/mL). Since two cases did not show sufficient recovery (their ALP levels were still high even though Ca and P levels returned to normal), vitamin D treatment (1000 IU/daily) has continued.

Eighty-nine (97.8%) episodes of seizures were generalized. Convulsion was localized in a single arm in two infants; laryngospasm was recorded in one infant. Most infants had more than one seizure before hospital admission.

Table 1: Biochemical values according to gender and patients' age at diagnosis

Sex	n (%)	Age (months)	C_a (mg/dL)	P (mg/dL)	ALP (U/L)	PTH (pg/mL)	25 OH vitamin D_3 (ng/mL)
Female	21 (23.1)	7.48 ± 5.16 (n = 21)	5.54 ± 0.90 (n = 21)	4.61 ± 1.82 (n = 21)	1574.2 ± 1168,6 (n = 21)	270.0 ± 181 (n = 20)	10.4 ± 4.8 (n = 9)
Male	70 (76.9)	5.57 ± 4.18 (n = 70)	5.55 ± 0.76 (n = 70)	4.82 ± 1.63 (n = 70)	1510.7 ± 847.5 (n = 69)	252.7 ± 152.1 (n = 66)	9.60 ± 5.19 (n = 29)
Total	91 (100)	6.01 ± 4.46 (n = 91)	5.55 ± 0.79 (n = 91)	4.77 ± 1.66 (n = 91)	1525.5 ± 925.4 (n = 90)	256.8 ± 158.3 (n = 86)	9.8 ± 5.0 (n = 38)

Ca = calcium, P = phosphorus, ALP = alkaline phosphatase, PTH = parathormone

Table 2: Classification of patients according to normal levels of biochemical data

Biochemical data	n	Measuring ranges	Category	n (%)
Calcium (mg/dL)	91	< 7.0	Low	91 (100.0)
Phosphorus (mg/dL)	91	< 3.8	Low	28 (30.8)
		3.8–6.5	Normal	(66.0)
		< 6.5	High	12 (13.2)
Alkaline phosphatase (U/L)	90	< 420	High	85 (94.5)
		145–420	Normal	5 (5.5)
25 (OH) vitamin D_3 (ng/mL)	38	< 20	Low	37 (97.3)
		20–50	Normal	1 (2.6)
Intact parathormone (pg/mL)	86	< 65	High	83 (96.5)
		9–65	Normal	3 (3.5)

Vitamin D deficiency was the main cause in all of the patients. None of the patients had received vitamin D prophylaxis during infancy and had been fed usually with breast or cow's milk. Frequent childbirth of the patients' mothers, and malnutrition in their children were recorded as previously suggested in the literature, and babies and their mothers did not benefit enough from the sunlight (16, 17). In a study of 50 children manifesting with hypocalcaemic seizures, 13 cases of exclusively breastfed infants were confirmed to have vitamin D deficiency (18). Seizures have been observed even on the first days of life (19). Hypocalcemic convulsions may be severe enough to cause fractures. Bilateral femoral fracture had been reported in a 17-year old male patient (20). None of the patients in this study had bone fractures.

Seizure due to congenital rickets is an unusual symptom during the first months of life. Hatun *et al* analysed

Table 3: Clinical and radiological findings of the patients by gender

Sex n (%)	Clinical signs None	Clinical signs Yes	Radiological signs None	Radiological signs Yes	Stage of rickets I	Stage of rickets III	Protein-energy malnutrition
Female 21 (23.1)	5 (27.8%) (n = 18)	13 (72.2%) (n = 18)	2 (22.2%) (n = 9)	7 (77.8%) (n = 9)	15 (71.5%)	6 (28.5%)	15 (100%) (n = 15)
Male (n = 56)	12 (21.5%) (n = 56)	70 (76.9) (n = 39)	10 (25.6%) (n = 39)	29 (74.4%)	46 (65.8%)	24 (34.2%)	11 (15.7%) (n = 70)
Total 91 (100)	17 (22.9%) (n = 74)	57 (77.1%) (n = 74)	12 (25%) (n = 48)	36 (75%) (n = 48)	61 (67.1%)	30 (32.9%)	26 (30.5%) (n = 85)

DISCUSSION

Hypocalcemia has been reported in the aetiology of neonatal convulsions for over a hundred years (9). The prevalence of neonatal convulsions was up to 33% in a large case series from Britain (10). Hypocalcaemic seizures are often generalized but can also appear as focal (11–13). While 89 (97.8%) episodes of seizures of the patients were generalized, convulsion in two infants was localized in a single arm.

It is not definitely known why anticonvulsant drugs have no effect in hypocalcaemic seizures. Calcium plays multiple roles in normal neuronal functions. Calcium acts to induce neurotransmitter release through stimulus-sensitive coupling. The graded release of neurotransmitters requires an inward current through voltage-gated calcium channels. Calcium is known to allow mobilization of synaptic vesicles by phosphorylating synapses that subsequently allow the vesicles to be freed from the neuronal cytoskeleton and move to the active zone channels (14).

In a retrospective clinical survey of epidemiologic and clinical features in infants and children diagnosed with nutritional rickets over the last 10 years, tetany and seizure were detected in infants below the age of six months, failure to thrive was present in those aged 6–12 months, and skeletal deformities were determined in infants above the age of 12 years, as the most frequently recorded presentations (15).

a total of 42 infants with vitamin D deficiency in the first three months of life and reported seizure (78.7%) as the major presentation (21). Convulsion was noted in all of the patients. This fact may be explained by the low education attainment and low socio-economic status of families living in the Eastern Anatolia region of Turkey. Twenty-five (27.3%) of the patients had protein-energy malnutrition.

Most patients in this study were admitted in winter (45%) and spring (30.7%). In our previous study, 31.7% of patients with hypocalcaemic seizures were seen in the spring, 11.0% in the summer, 20.7% in autumn and 36.6% in winter, frequently in January (2).

In the treatment of hypocalcaemia, calcium replacement is done. Typically, treatment with anticonvulsant drugs is not needed (9, 12). To maintain normocalcaemia, a continuous intravenous infusion of calcium (as elemental calcium, 20–80 mg/kg/24 hours) is preferable over frequent boluses as long as there is good intravenous access, since a large fraction of the calcium content in the bolus is lost in the urine during the infusion (22). Vitamin D should be given to infants with vitamin D deficiency rickets. The first regimen consists of daily therapy with 3000–5000 IU orally. An alternative treatment option in non-compliant patients or those without follow-up is "Stosstherapy"; a dose of 600 000 IU of vitamin D is given orally in a single day if this method is chosen (23). However, a dose of 150 000 IU or 300 000 IU

of vitamin D is adequate for the treatment of vitamin D deficiency rickets; moreover, 600 000 IU of vitamin D may carry the risk of hypercalcaemia (24). Also, no statistically significant difference was found among the four different treatment options [150 000 IU, 300 000 IU, 2000 IU for five to six months, and 5000 IU of vitamin D per day for three months] (2).

Initial finding in all of the patients was convulsion. All of them presented for the first time to a health centre with convulsions. None of them had been identified with hypocalcaemia in their routine controls or suffered convulsion thereafter. None of the patients developed convulsions after initial treatment.

The Ministry of Health of Turkey started a campaign in May 2005 to give free vitamin D supplements to all infants from 0–12 months across the country to eliminate nutritional rickets. Free vitamin D drops are distributed through health centres. According to clinical observations, the number of patients presenting with hypocalcaemic convulsions has declined in recent years.

The incidence of nutritional rickets in the 8631 children under three years of age in Eastern Anatolia in 1998 was found to be 6%; in 2011, the incidence was found to be 3.1% of 946 patients between four months and 15 years (2, 3). However, because of inadequate education of parents, a sufficient amount of vitamin D drops was not used. Therefore, we still encounter infants with rickets.

CONCLUSION

Vitamin D deficiency or nutritional rickets may present with convulsion without leading to evident clinical signs in infancy. Thus, although there are no clinical signs of rickets in hypocalcaemic infants, rickets should be considered and infants investigated for vitamin D deficiency; if the deficiency is confirmed, we wish to emphasize the need for vitamin D treatment.

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