TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2009; 39 (1): 1-4
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0805-54

The Clinical and Laboratory Characteristics of Vitamin D Intoxication in Children

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Aim: In this retrospective study, patients with vitamin D intoxication (VDI) were evaluated with respect to clinical and laboratory characteristics, treatment protocols and complications.

Materials and Methods: The medical records of 27 children with VDI between 2003 and 2008 were investigated. Data included age, gender, nutritional status, dose and duration of prophylactic/therapeutic vitamin D, the reasons for vitamin D therapy prescription, clinical signs and symptoms, laboratory findings, therapy protocol for VDI, and complications.

Results: The mean dose of vitamin D prescribed to the patients was 600,000 U (range: 300,000-1,200,000 U). The most prominent reason (80.9%) for physician prescription of vitamin D therapy was delay in achievement of developmental milestones, which may also be seen in vitamin D-deficient rickets (VDDR). Clinical manifestations of the patients with VDI were vomiting (85.7%), anorexia (57.1%), weight loss (47.6%), dehydration (42.8%), polyuria/polydipsia (38%), and constipation (33.3%). Biochemical parameters of the patients at admission were as follows: mean serum total calcium 12.1 ± 2.8 mg/dl, phosphorus 6.1 ± 1.2 mg/dl, alkaline phosphatase 351 ± 224 IU/L, 25 hydroxyvitamin D (25[OH]D) 247 ± 117.8 ng/ml, intact parathyroid hormone (PTH) levels 15 ± 9.2 ng/ml, and urine calcium/creatinine ratio 2.47 ± 1.03. There was negative correlation between the serum 25[OH]D and PTH levels ($r = -0.84$, $P < 0.001$). Six patients with severe hypercalcemia (serum total calcium: >15 mg/dl) were controlled with bisphosphonate therapy. Nephrocalcinosis developed in seven patients (25.9%). All patients were followed up at three-month intervals for 1.3 years after treatment. Hypercalcemia did not recur and nephrocalcinosis persisted in all except one case.

Conclusions: The diagnosis of VDDR without checking serum 25[OH]D level may cause redundant treatment that leads to VDI. All patients who are clinically suspected of VDDR should be checked for serum vitamin D status and questioned for previous vitamin D administration before starting vitamin D therapy.

Key Words: Vitamin D intoxication, children

Çocuklarda Vitamin D Zehirlenmesinin Klinik ve Laboratuvar Özellikleri

Amaç: Bu retrospektif çalışmada, vitamin D zehirlenmesi (VDZ) olan hastalar klinik ve laboratuvar özellikleri, tedavi protokolleri ve gelişen komplikasyonlar bakımından değerlendirildiler.

Yöntem ve Gereç: 2003-2008 yılları arasında VDZ tanısı konulan 27 vakanın medikal kayıtları incelendi. Vakalar yaş, cins, beslenme durumu, profilaktik veya tedavi maksatlı uygulanan vitamin D'nin doz ve süresi, vitamin D'nin neden reçete edildiği, hastalığın klinik belirti ve bulguları, laboratuvar bulguları, tedavi protokolleri ve gelişen komplikasyonlar bakımından değerlendirildiler.

Bulgular: Vakalara reçete edilen ortalama vitamin D dozu 600.000 U (300.000-1.200.000 U) idi. Doktorların vitamin D reçetesi yazmalarının en önde gelen nedeni vitamin D eksikliğine bağlı riketsli çocuklarda da rastlanan gelişim basamaklarındaki gecikme idi (% 80.9). Vakaların klinik belirti ve bulguları ise kusma (% 85.7), iştahsızlık (% 57.1), kilo kaybı (% 47.6), susuzluk (% 42.8), çok su içme/çok işeme (% 38) ve kabızlık (% 33.3) idi. Başvuru sırasında elde edilen biyokimyasal parametreler arasında ortalama serum total kalsiyum, fosfor, alkalen fosfataz, 25-hidroksi vitamin D (25[OH]D), intakt paratiroid hormon ve idrar kalsiyum/kreatinin düzeyleri sırası ile 12.1 ± 2.8 mg/dl, 6.1 ± 1.2 mg/dl 351 ± 224 IU/L, 247 ± 117.8 ng/ml, 15 ± 9.2 pg/ml, and 2.47 ± 1.03 idi. Serum 25[OH]D ve PTH düzeyleri arasında negatif bir korelasyon saptandı ($r = -0.84$, $P < 0.001$). Altı olguda saptanan ciddi hiperkalsemi (serum total kalsiyum: > 15 mg/dl) bifosfonat tedavisi ile düzeldi. Vakaların 7'sinde (% 25.9) nefrokalsinozis gelişti. Tedaviden sonra, tüm vakalar 3 aylık periyotlar ile 1.3 yıl boyunca takip edildiler. Hiperkalsemi tekrar ortaya çıkmadı ve bir vaka dışında diğer tüm olgularda nefrokalsinozis durumunun devam ettiği saptandı.

Sonuç: Serum 25[OH]D düzeyini kontrol etmeden konulan vitamin D eksikliğine bağlı rikets tanısı, VDZ ile sonuçlanan gereksiz vitamin D tedavisine neden olabilir. Klinik olarak vitamin D eksikliğinden şüphe edilen vakalarda vitamin D tedavisi reçete edilmeden önce serum vitamin D düzeyi ölçülmeli ve önceden vitamin D tedavisi uygulanıp uygulanmadığı sorgulanmalıdır.

Anahtar Sözcükler: D vitamini zehirlenmesi, çocuklar

Received: May 21, 2008
Accepted: September 03, 2007

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Introduction

Hypervitaminosis D is characterized by high serum levels of 25-hydroxyvitamin D (25[OH]D) and hypercalcemia or hypercalciuria, or both (1). It may cause serious complications such as calcification of the soft tissues (particularly the kidneys and heart), changes in the central nervous system, and in severe cases, death (2-5). Hypervitaminosis D in children may result from disorders of vitamin D metabolism such as subcutaneous fat necrosis and sarcoidosis, or vitamin D toxicity (6). However, the majority of the patients with vitamin D toxicity results from excess amount of oral intake or parenteral administration of vitamin D, even though the exact toxic dose of vitamin D remains unknown.

The aim of this retrospective study was to analyze the children diagnosed with vitamin D intoxication (VDI) in terms of the given doses of vitamin D, clinical and laboratory characteristics and final outcomes.

Materials and Methods

The medical records of children diagnosed with VDI between 1 January 2003 and 31 December 2008 were investigated. Data included age, gender, nutritional status, dose and duration of prophylactic/therapeutic vitamin D, the reasons for vitamin D therapy prescription, serum level of 25[OH]D before vitamin D therapy, clinical signs and symptoms, laboratory findings, therapy protocol for VDI, and complications. Laboratory investigations included complete blood count; urine analysis; renal and liver function tests; total protein, albumin, serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), intact parathyroid hormone (iPTH) and 25[OH]D levels; electrocardiographic analysis; and renal ultrasonography.

Results

A total of 27 cases with VDI were recruited into the study. Median age of the cases was 12.8 months (range: 1-22 months). Seventeen (62.9%) of the patients were male. Thirteen (48.1%) of the cases had been fed breast-milk plus additional food by the time of diagnosis. The rest had been fed breast-milk plus formula (n=8, 29.6%) or formula plus additional food (n=6, 22.2%). Twenty-one of the 27 patients (77.7%) had been taking prophylactic vitamin D 400 U a day. Median duration of prophylactic vitamin D administration was 9.5 months (range: 1-17 months). The most prominent reason (80.9%) for vitamin D prescription was failure to achieve developmental milestones such as delay in sitting, walking, hypotonia, and delayed eruption of teeth, which may also be seen in vitamin D-deficient rickets (VDDR). As far as could be ascertained from the medical history of the patients, serum 25[OH]D level had not been measured before the vitamin D therapy. All of the patients were prescribed a total of 1-4 ampoules of vitamin D (one ampoule contains 300,000 U vitamin D) by previous physicians. The average dose of vitamin D therapy was approximately 600,000 U (range: 300,000-1,200,000 U). The clinical manifestations were vomiting (85.7%), anorexia (57.1%), weight loss (47.6%), dehydration (42.8%), polyuria/polydipsia (38%), and constipation (33.3%). Total protein and albumin levels were normal in all cases. Mean serum total Ca, P, ALP, iPTH, and 25[OH]D levels, and urine calcium/creatinine ratio at admission and sixth months are shown in Table 1. Mean serum total Ca and 25[OH]D concentrations of the patients were 12.1 ± 2.8 mg/dl (N: <11 mg/dl) and 247 ± 117.8 ng/ml (N: <40 ng/ml). As shown in Figure 1, there was a negative correlation between the serum vitamin D and PTH levels ($r=-0.84$, $P < 0.001$). All patients had hypercalciuria, but severe hypercalcemia occurred in only 6 cases (22.2%), who were hospitalized and successfully treated with bisphosphonates in addition to intravenous hydration and furosemide therapy. The average duration of hospitalization was 9 days (range: 7-12 days). Nephrocalcinosis was the only complication diagnosed in 7 patients (25.9%). All cases were followed at three-month intervals for at least 1.3 years and hypercalcemia did not recur, although nephrocalcinosis persisted in all patients with only one exception.

Table. Biochemical characteristics of the patients with vitamin D intoxication.

Parameters	At admission	At sixth month
Ca (mg/dl)	12.1 ± 2.8	9.6 ± 0.5
P (mg/dl)	6.1 ± 1.20	4.1 ± 0.5
ALP (IU/L)	351 ± 224	538 ± 128
PTH (pg/ml)	15 ± 9.2	48 ± 41
25(OH)D (ng/ml)	247 ± 117.8	110.2 ± 72
Ca/Cr	2.47 ± 1.03	0.11 ± 0.12

Ca: Calcium. P: Phosphorus. ALP: Alkaline phosphatase.
PTH: Parathyroid hormone. Ca/Cr: Urine calcium/creatinine ratio.

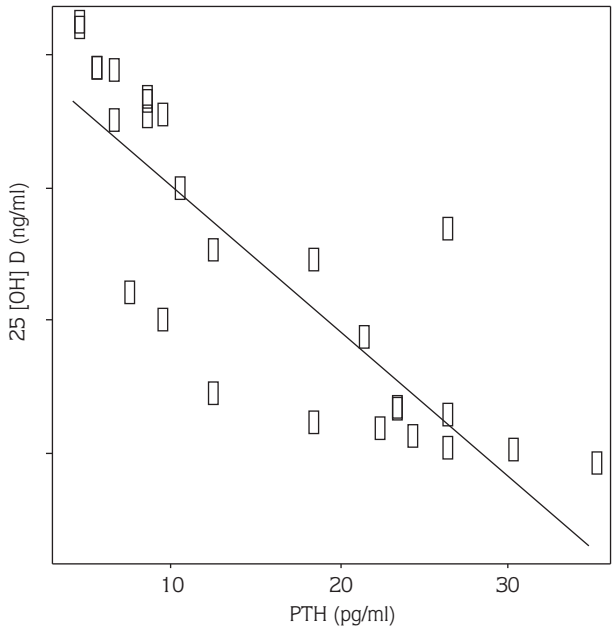

Figure. Correlation between 25 (OH) D and PTH (r=-0.84, P < 0.001).

Discussion

Our results clearly demonstrated that 27 infants developed VDI due to prescription of excess vitamin D to patients in whom VDDR was diagnosed based on clinical findings alone, without measuring the serum 25[OH]D level. VDDR was mostly diagnosed between 3 and 18 months of age (7,8). As is known, especially if mothers have sufficient vitamin D levels, vitamin D metabolites protect breast-fed infants from vitamin D deficiency for the first 3 months of life (9). Therefore, maternal vitamin D deficiency, exclusive breast-feeding, living in temperate climates (latitude above 40°), inadequate sunlight exposure, and darkly pigmented skin are accepted as important risk factors in the pathogenesis of vitamin D deficiency (8,10). To prevent VDDR, many guidelines by the Centers for Disease Control and Prevention (CDC) and the European Society of Pediatric Endocrinology (ESPE) have acknowledged that infants should receive at least 400 U of vitamin D daily (in northern communities, 800 U) until they reach one year of age or their daily diet includes at least 400 U of vitamin D from other dietary sources (11-13). In addition, one should remember that another source of vitamin D for infants is fortified formulas or milk with vitamin D. Formulas or milk containing 40 U vitamin D per 100 g can usually meet the requirement of 400 U/day. In this study, 21 of 27 patients were regularly receiving prophylactic vitamin D. Fourteen patients were being fed a formula that met the daily requirement of vitamin D. These findings suggest that the parents of patients are insufficiently questioned regarding vitamin D deficiency. However, it was reported that VDI would not develop unless vitamin D was received above the supplemental dose of 2000 U/day (14).

Even though VDDR is a common problem in the East Anatolian region of Turkey (15), serum 25[OH]D level, which is crucial for certain diagnoses, cannot be measured yet in most of the local medical centers. Thus, the diagnosis of VDDR has been based only on clinical findings. On the other hand, because VDDR is a disease of the growing child, clinical manifestations may show variability with respect to the childhood period in which diagnosis of rickets is made. Orhan (16) reported that sensitivity, positive predictive value and negative predictive value of physical findings of VDDR in infancy were 65.7%, 60.9% and 74.6%, respectively. In that study, it was concluded that clinical signs of VDDR were not specific at least in infancy, and that diagnosis of VDDR should not be based only on physical findings. It can be inferred from these results that physical findings in the diagnosis of VDDR during infancy are insufficient for prescribing vitamin D therapy that could lead to VDI. Furthermore, high doses of vitamin D had been administrated several times to the patients who participated in our study. This finding suggests that physicians did not interrogate parents regarding previous medical history of the patients before beginning vitamin D therapy.

The cut-off value for vitamin D toxicity has not yet been established by age groups. However, in children, intake of as little as five times the recommended dietary allowance of 400 U per day has been associated with toxicity (17). In this study, average dose of vitamin D therapy was approximately 600,000 U, an amount as high as 300 times the upper limit of the toxic dose (2000 U) (11). As shown in Table 1, in this study, mean serum 25[OH]D level at admission was much higher than the upper limit reference value reported in the literature (18). There were negative correlations between the serum vitamin D and PTH levels (Figure). These results were consistent with VDI.

Severe hypercalcemia occurred in only six (22.2%) cases, who were hospitalized and successfully treated by

bisphosphonates in addition to intravenous hydration and furosemide therapy. In recent years, alendronate, an oral bisphosphonate, has been added to the therapy of hypercalcemia secondary to VDI in children (19). In this study, we used oral alendronate therapy in three patients and intravenous pamidronate therapy in the rest of the patients with severe hypercalcemia. The average hospitalization duration was 9 days (range: 7-12 days).

In this study, although hypercalciuria occurred in all patients, nephrocalcinosis developed in only seven cases. We monitored the patients who developed nephrocalcinosis at three-month intervals for at least 1.3 years. Hypercalcemia did not recur after treatment (Table). During follow-up, nephrocalcinosis persisted in all patients except one. The complete recovery of nephrocalcinosis may take several years even after the underlying condition is removed (20).

In conclusion, all patients who are suspected of VDDR with clinical findings should be checked for serum vitamin D status and questioned regarding previous vitamin D administration before starting vitamin D therapy. The diagnosis of VDDR based on clinical grounds alone without checking serum 25[OH]D level may cause redundant treatment that leads to VDI.

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