Case Report:
Vitamin D Intoxication in Three Children With Varied Manifestations: A Case Series and Review

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ABSTRACT

Background: Inadvertent and erroneous prescription of vitamin D beyond the recommended dosage and route of administration can cause vitamin D intoxication in children. Infants are particularly vulnerable to such toxicity. Clinical features are due to hypercalcemia, ranging from mild to life-threatening symptoms. We report two infants and one child who had varied manifestations due to hypercalcemia resulting from empirical treatment with high doses of vitamin D. We discuss the management strategies in these cases along with a brief review of the literature.

Case Presentation: Our first case was a 10-month-old infant who presented with fever, vomiting, and failure to thrive. Our detailed clinical examination and investigation revealed hypertension and bilateral nephrocalcinosis along with urinary tract infection. The second child was a 2-year-old girl with severe hypercalcemia with clinical features mimicking acute bacterial meningitis. The third infant had mild symptoms like constipation and irritability, and investigations showed moderate hypercalcemia. All had a history of inappropriate vitamin D administration, either in oral or parenteral form, and they were all successfully treated.

Conclusions: These case series highlight the importance of proper dosage, avoidance of parenteral route, along with appropriate clinical and biochemical monitoring during the course, whenever a dose of vitamin D is advised.

1. Introduction

Over the past decade, Vitamin D Deficiency (VDD) has been recognized more frequently in India among children, causing an increased burden of health hazards and expenditure despite adequate sunshine in this sub-continent [1]. Increasing awareness about the high prevalence of VDD has caused widespread use of oral vitamin D supplements with occasional high parenteral doses, given empirically on the clinical ground only. Infants often receive such treatment for nonspecific complaints like failure to thrive, delayed dentition or walking, and physiological genu valgus. This high dose results in Vitamin D Intoxication (VDI). The reasons for such practice are high laboratory cost and...
the non-availability of the test widely [2]. The increased calcium absorption from the intestine and bone resorption due to vitamin D overdose can cause hypercalcemia and hypercalciuria resulting in nephrocalcinosis, urolithiasis, and other soft tissue calcifications [3]. Here we describe three children diagnosed with VDI and different manifestations due to unsupervised administration of very high doses of vitamin D over a long period. This case series warns against indiscriminate use of a mega-dose of vitamin D in parenteral and oral form by practicing pediatricians.

2. Case Presentations

Case 1

A 10-month-old male infant with Severe Acute Malnutrition (SAM) and delayed motor development was admitted with complaints of fever and vomiting for 7 days and not growing well for the last 6 months. He was exclusively breastfed up to four months of age. On physical examination, he was febrile, pale with generalized muscle wasting, and without any signs of dehydration. He had tachycardia (Heart Rate, HR = 120 beat/min) and was hypertensive (Blood Pressure, BP >95th percentile). The other systemic examination findings were unremarkable. He was clinically diagnosed with SAM with probable sepsis and renovascular hypertension.

Laboratory investigations revealed microcytic hypochromic anemia, normal serum electrolytes, and renal function tests (Table 1). Renal ultrasonography was done because of the presence of hypertension, which showed bilateral grade 2 medullary Nephrocalcinosis (NC), to our surprise (Figure 1) [4]. Further biochemical test results showed severe hypercalcemia with normal phosphorus, low Parathormone (PTH), very high serum 25(OH) D (25 Hydroxy-cholecalciferol), and hypercalciuria, suggestive of VDI. Liver function tests and serum amylase were within the normal range. Radiograph of the wrist with elbow, Electrocardiogram (ECG), and echocardiography did not show any abnormality. Urine culture grew Citrobacter freundii. On detailed inquiry, it was revealed that the baby had received vitamin D in a cumulative dose of 7200000 IU over three months (injection of vitamin D 600000 IU weekly IM) prescribed by a practicing physician for vomiting for 7 days. The child responded, and serum calcium dropped to 12 mg/dL. He required a total of three doses of oral alendronate before discharge when serum calcium was 10.5 mg/dL. As the hypertension was controlled, we were advised to continue with oral furosemide and asked for a follow-up. After 15 days, the child was readmitted with polyuria and hypercalcemia. This time he was treated successfully with six doses of oral alendronate. After six months, the baby is normotensive, normocalcemic but with persistent medullary nephrocalcinosis.

Case 2

A 2-year-old girl was admitted with complaints of fever for 10 days, poor feeding, irritability, lethargy, and headbanging for the last two days. On clinical examination, she was conscious but irritable, drowsy, febrile, normotensive with some dehydration. CNS examination showed doubtful meningeal signs and depressed deep tendon reflexes. Other systemic examination findings were normal.

The child was managed as a case of acute bacterial meningitis as per protocol. Arterial blood gas analysis revealed high ionized calcium (3.2 mmol/L) with normal pH and bicarbonate level. Serum calcium level was 31.9 mg/dL. Other biochemical test results were obtained, which are listed in Table 1. Her urine culture grew E. coli which was sensitive to amikacin. Suspicious of the severe hypercalcemia, detailed medication history was sought. He was found to have received 1800000 IU of vitamin D (600000 IU, IM weekly for 3 weeks) before presentation, prescribed by a practicing physician for poor weight gain. She was diagnosed with iatrogenic VDI and started on aggressive fluid therapy (150 mL/kg/d) along with intravenous furosemide (2 mg/kg/d) in divided doses. Injection hydrocortisone (1 mg/kg/d) was added, and intranasal calcitonin spray was given at a dose of 200 IU twice daily, due to unavailability of the parenteral form of calcitonin. After 48 hours, the sensorium improved, and the child became afebrile. Serum calcium came down to 15.4 mg/dL with normal renal parameters. Intranasal calcitonin was stopped after six doses. But due to rebound hypercalcemia, oral alendronate (5 mg/d) was added to the regimen. It was continued for three days, which resulted in a drop in serum calcium level. At discharge, her serum calcium was 11.5 mg/dL.

Breastfeeding was withheld temporarily, and all medications containing vitamin D and calcium were stopped. During this treatment, he was monitored regularly for improvements in symptoms, urine output, and serum calcium level. Due to persistent hypercalcemia, oral alendronate was added at a dose of 5 mg/d after three days. The child responded, and serum calcium dropped to 12 mg/dL. He required a total of three doses of oral alendronate before discharge when serum calcium was 10.5 mg/dL. As the hypertension was controlled, we were advised to continue with oral furosemide and asked for a follow-up. After 15 days, the child was readmitted with polyuria and hypercalcemia. This time he was treated successfully with six doses of oral alendronate. After six months, the baby is normotensive, normocalcemic but with persistent medullary nephrocalcinosis.
mg/dL. She was advised to continue oral alendronate for another seven days (alternate day) with regular follow-up. After two weeks, her serum calcium was 9.8 mg/dL. She was on regular follow-up for the last year and maintained normocalcemia.

Case 3

An 11-month-old boy, a known case of recurrent wheeze, admitted with complaints of irritability, poor feeding, and constipation for the last 15 days. He was exclusively breastfed till six months of age, with the introduction of semisolid food and cow’s milk after that. He was on supplementation of a multivitamin drop at a dose of 0.5 mL daily (containing vitamin D 200 IU) along with vitamin D3 800 IU/d for 15 days of life. The cumulative dose of vitamin D thus received was approximately 300000 IU till the time of presentation. Investigations revealed normal blood counts and electrolytes except hypercalcemia and a high vitamin D3 level (Table 1). A diagnosis of VDI was made and treated by removing the exogenous source, withholding breastfeeding, calcium restricted diet, diuresis with normal saline (1.5 times), and oral furosemide. After 48 hours, her serum calcium levels returned to normal, and he was discharged after three days.

3. Discussion and Review of Literature

For this review, citations were identified through PubMed search, limited to the last 15 years using the keywords “vitamin D toxicity” OR “vitamin D intoxication” OR “vitamin D poisoning” AND “child” OR “infant” AND “nephrocalcinosis”. Additional articles were identified from the reference list of identified papers. Only relevant papers in the English language were taken into consideration.

The exact incidence of VDI is unclear due to the lack of systematic studies addressing this issue. There are reports of this toxicity in children from developed and developing countries [5, 6]. Since the first description of VDI in an Indian infant in 2004, it has been reported across the country [6-8]. As per the global consensus recommendations on prevention and management of nutritional rickets, vitamin D deficient children (0-18 years) should be treated with vitamin D2 or vitamin D3 2000 IU/d for at least 12 weeks along with oral calcium 500 mg/d regardless of age and weight [9]. In children suspected to have VDD, the Indian Academy of Paediatrics (IAP) recommends a daily intake of 2000 IU of vitamin D along with 500 mg of calcium in infants and 3000-6000 IU of vitamin D with 600-800 mg of calcium in children in the age group of 1-18 years, for 3 months [10]. If larger doses are to be given, then 60000 IU of vitamin D weekly for 6 weeks, preferably in oral form, is recommended. Intramuscular vitamin D should only be administered to children with rickets having severe malabsorption.

The relationship between the amounts of vitamin D intake causing excess or toxicity and the corresponding severity of hypercalcemia have not been well studied in the pediatric age group. It has been found that intake of 50000 units of vitamin D or more can result in its poisoning in a person having normal parathyroid function and vitamin D metabolism [11]. Our first and second patients had received very high doses of vitamin D intramuscularly, whereas the third child had taken it orally. Serum vitamin D3 or 25(OH) D levels up to 100 ng/mL are considered safe for children and adults. In contrast, a level above 150 ng/mL is usually associated with VDI [12], evident from the first two cases. Though our third case had a vitamin D3 level of only 138 ng/mL, he still had symptomatic hypercalcemia. This can be explained by genetic polymorphism, which regulates the synthesis and metabolism of vitamin D, vitamin D binding protein, and the severity of hypercalcemia. In a study from Iran, 15 children younger than 12 years presented to the pediatric emergency department with a history of ingestion of more than 1500 IU/d of vitamin D supplements. The Mean±SD ingested dose was 406700.7±227400.1 IU. Only one child had hypercalcemia, and eight had vitamin D levels more than 100 ng/mL. This study concluded that acute vitamin D toxicity might be a benign condition in Iranian children due to the high prevalence of vitamin D deficiency [13].

In a study in Turkey, authors found that 70% of their VDI patients have received multiple doses of vitamin D periodically due to wrong dose, most commonly prescribed for the nonspecific complaints, including delayed walking or tooth eruption, which was also found in our cases [14]. Joshi retrospectively studied seven children (six female, one male), aged between 7.5 and 25 months with hypervitaminosis D, who had taken vitamin D (900000-4000000 IU) prescribed by medical practitioners for wrong indications like failure to thrive [6]. The clinical features were constipation, loss of appetite, lethargy, polyuria, and dehydration. Hypercalciuria was present in all cases, whereas nephrocalcinosis was seen in five children. Hypercalcemia usually presents nonspecific symptoms like poor appetite, pain abdomen, vomiting, constipation, muscle weakness, bone pain, polyuria, and dehydration. As evident from the first two cases, VDI can be a differential diagnosis in children presenting with clinical features of sepsis or acute bac-
terial meningitis. Hence a detailed medication history can clinch the diagnosis in such cases. Furthermore, the first baby had hypertension at presentation, which was reported as an unusual manifestation of VDI in infants elsewhere. This can be explained by renal pathology and vascular calcification [15]. Nephrocalcinosis (NC) is a well-known complication of VDI, seen in 10%-25% of cases due to the deposition of calcium salts in tubular cells of the loop of Henle and basement membrane epithelium [6, 16]. These are classically distributed along the corticomedullary junction, which can be detected easily in ultrasonography than in plain radiography or Computed Tomography (CT) [8, 17]. In a Taiwan study, 5 out of 16 children (31%) with nephrocalcinosis had a history of vitamin D intoxication [18].

Hypercalcemia is classified according to serum calcium level as mild (<12 mg/dL), moderate (12-14 mg/dL), and severe (>14 mg/dL) [16]. Our first and second patient had severe hypercalcemia (14.8 mg/dL, 31.2 mg/dL) and very high 25(OH)D level (>150 ng/mL). To our knowledge, hypercalcemia to the extent of 31.2 mg/dL had never been reported in the literature in children with VDI. Severe hypercalcemia needs emergency intervention due to its widespread multisystem adverse effects, including death, which demands rapid correction.

The treatment of VDI mainly aims to manage symptomatic hypercalcemia, which results from increased intestinal absorption of calcium and from the direct effect of 1, 25 di-hydroxy vitamin D to increase resorption of bone. There are no national or international guidelines available for the management of VDI. Treatment options available in children currently include discontinuation of vitamin D intake, intravenous hydration with normal saline, furosemide, glucocorticoids, calcitonin, alendronate, pamidronate, and hemodialysis, mainly based on case reports and small studies [14].

Primary treatment of symptomatic hypercalcemia is aggressive fluid therapy with normal saline at 1.5-2.5 times maintenance along with loop diuretics to increase the urinary flow and calcium excretion [19]. Corticosteroids and calcitonin can be added in non-responsive cases. Glucocorticoids decrease both intestinal absorption and renal reabsorption of calcium. However, the onset of action may take up to 3 days, and they are less efficient in “severe hypercalcemia” [9, 14]. Due to inherent nephrocalcinosis and persistent hypertension, we did not recommend steroids in the first case. The third case was managed with IV fluids and loop diuretics only, as it was a mild variant. Calcitonin is a hormone that directly inhibits osteoclast function. Though it has a rapid effect on serum calcium, its therapeutic uses are limited due to tachyphylaxis and reports of anaphylactic shock. We used calcitonin in the form of nasal spray in the second child due to the presence of severe hypercalcemia. Bisphosphonates can successfully control hypercalcemia by osteoclast apoptosis and its anti-resorptive action on bone.

We treated the first two cases with oral alendronate successfully. Alendronate as the first-line treatment for VDI in an infant was first described in 2003, where the patient required a total of 30 mg to achieve normocalcemia [5]. In a recent series, alendronate achieved normocalcemia four times faster than prednisolone, including reduced hospital stay [20]. But another study showed recurrence of hypercalcemia in children on follow-up who received only alendronate in addition to IV...
fluid and loop diuretics (3 out of 11), as in our first case [14]. Though there are reports of resolution of NC by a few authors, complete resolution may not be seen even after a follow-up of 1-13 years [21, 22]. Our first patient had persistent NC at 6 months follow-up. Because of the long half-life of vitamin D, regular monitoring of symptoms and serum calcium levels in patients with VDI is highly recommended.

### Table 1. Haematological, biochemical and radiological findings of three children with vitamin D intoxication

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case 1 (10 Months)*</th>
<th>Case 2 (2 Years)*</th>
<th>Case 3 (11 Months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dL)</td>
<td>10.2 (10.5-14)</td>
<td>11.6 (11.5-14.5)</td>
<td>10.5 (10.5-14)</td>
</tr>
<tr>
<td>TLC (x 10³/mL)</td>
<td>12.3 (6-14)</td>
<td>18.89 (4-12)</td>
<td>10.5 (6-14)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135 (134-144)</td>
<td>140 (134-143)</td>
<td>140 (134-144)</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>5 (3.5-6.1)</td>
<td>3.9 (3.3-4.6)</td>
<td>3.9 (3.5-6.1)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98 (98-106)</td>
<td>102 (98-106)</td>
<td>96 (98-106)</td>
</tr>
<tr>
<td>Bicarbonate (meq/L)</td>
<td>22 (21-28)</td>
<td>23 (21-28)</td>
<td>24 (21-28)</td>
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<tr>
<td>Calcium (mg/dL)</td>
<td>14.8 (8.8-10.8)</td>
<td>31.9 (8.8-10.8)</td>
<td>12.2 (8.8-10.8)</td>
</tr>
<tr>
<td>Ionised calcium (mmol/L)</td>
<td>2.6 (1.12-1.23)</td>
<td>3.2 (1.12-1.23)</td>
<td>1.2 (1.12-1.23)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5 (3.8-6.5)</td>
<td>2.8 (3.8-6.5)</td>
<td>4.2 (3.8-6.5)</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>2.5 (1.6-2.6)</td>
<td>1.9 (1.6-2.6)</td>
<td>2.4 (1.6-2.6)</td>
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<tr>
<td>AST (U/L)</td>
<td>42 (22-63)</td>
<td>56 (20-60)</td>
<td>48 (22-63)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>38 (12-45)</td>
<td>28 (5-45)</td>
<td>32 (12-45)</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>95 (82-283)</td>
<td>78 (104-345)</td>
<td>250 (82-283)</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.8 (1.9-4.9)</td>
<td>3.2 (3.4-4.2)</td>
<td>3.6 (1.9-4.9)</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>4.84 (7-53)</td>
<td>2.8 (7-53)</td>
<td>5.2 (7-53)</td>
</tr>
<tr>
<td>25 (OH) D (ng/mL)</td>
<td>&gt;150 (25-80)</td>
<td>&gt;150 (25-80)</td>
<td>132 (25-80)</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>38 (5-18)</td>
<td>46 (5-18)</td>
<td>32 (5-18)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.32 (0.03-0.50)</td>
<td>0.48 (0.03-0.50)</td>
<td>0.25 (0.03-0.50)</td>
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<tr>
<td>Urine calcium creatinine ratio</td>
<td>2.33 (0.2-0.6)</td>
<td>0.8 (&lt;0.2)</td>
<td>1.2 (0.2-0.6)</td>
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<tr>
<td>CSF cytology, biochemical, C/S</td>
<td>Normal, No growth</td>
<td>Normal, No growth</td>
<td>Not done</td>
</tr>
<tr>
<td>ECG</td>
<td>Normal</td>
<td>QT interval shortening, ST elevation</td>
<td>Normal</td>
</tr>
<tr>
<td>Skeletal survey</td>
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<td>Not done</td>
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<tr>
<td>Neuroimaging</td>
<td>Normal</td>
<td>Normal</td>
<td>Not done</td>
</tr>
</tbody>
</table>

*Age-appropriate values are inside the parenthesis.


4. Conclusion

Iatrogenic vitamin D toxicity is not uncommon in children due to its indiscriminate use and prescription of very high dosage, particularly in parenteral form by medical practitioners for nonspecific complaints. Infants and children with severe malnutrition are more susceptible to it. Before recommending mega doses of vitamin D, its deficiency should be confirmed by appropriate...
laboratory tests. Parents should always be explained regarding the adverse effects of such therapy and the importance of regular follow-up. In the current scenario, there is a dire need for creating awareness among practitioners against unsupervised empirical treatment for VDD to prevent such menace.

**Ethical Considerations**

**Compliance with ethical guidelines**

The study was conducted as per the ethical guidelines of the Institutional Ethics Committee, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India, and informed consent was taken from the parents for publication of data.

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**Authors’ contributions**

All authors equally contributed to preparing this article.

**Conflicts of interest**

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