Stosstherapy for Treatment of Vitamin D Deficiency Rickets

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Calcipenic rickets refers to deficient bone mineralization of the growth plates due to calcium deficiency, either caused directly by dietary deficiency or secondarily by vitamin D deficiency. Different methods of treating vitamin D deficiency have been advocated, ranging from small doses for a few months to a single mega dose, an approach referred to as *stosstherapy*. Stosstherapy has been recommended especially when compliance is in question. This article presents the case of a child with severe vitamin D deficiency who was treated successfully with stosstherapy.

CASE PRESENTATION

Initial Presentation and History

A 16-month-old African-American boy who had been previously healthy presented to the emergency department of an inner city hospital in New York with bilateral carpopedal spasms. His mother noticed that he seemed sleepier and less active than usual. There was no history of seizures, diarrhea, vomiting, or fever.

Dietary history revealed that he had been breastfed without vitamin D supplementation. His pediatrician prescribed multivitamins containing vitamin D, but the prescription was not filled. Multiple attempts by the mother to switch him to formula or regular milk were unsuccessful. At age 5 months, he was started on cereal and was currently eating regular table food. He was also eating about 4 ounces of yogurt daily. The mother's nutritional status during pregnancy and lactation was not known.

He had played outside during the warmer months, and he presented with the above symptoms in the fall. The patient's mother reported that he had developmental delays in mobilization: he crawled at age 13 months and started to cruise at age 15 months.

Physical Examination

On examination, the child's height was 27.8 in (70.5 cm) and he weighed 17.9 lb (8.13 kg), which placed him below the third percentile. His head circumference was 18.5 in (47 cm), which was within the 25th percentile. His growth curve revealed failure to thrive. The patient had frontal bossing and widening of the wrists and ankles, prominent costochondral junctions in the chest, and delayed dentition. The anterior fontanel was closed. Trousseau's sign was positive.

Laboratory and Imaging Studies

Laboratory studies revealed decreased levels of serum calcium, ionized calcium, and serum phosphorus at 4.9 mg/dL, 3.12 mg/dL, and 3.4 mg/dL, respectively, as well as increased serum alkaline phosphatase at 3949 U/L (**Table 1**). Serum albumin, magnesium, aspartate aminotransferase, and alanine aminotransferase levels were normal. An electrocardiogram revealed a prolonged QTc interval of 0.488 sec (normal, < 0.44 sec), but no arrhythmias were noted. Radiography of the patient's hands and wrist revealed changes typical of rickets, including cupping and fraying of the distal ends of long bones (**Figure 1**).

Treatment

The patient was admitted to the pediatric intensive care unit and was given 3 doses of calcium gluconate 600 mg intravenously (75 mg/kg per dose). Tetany resolved, and the QTc interval normalized. He was then started on oral calcium carbonate (75 mg/kg/day of elemental calcium). Once eucalcemia was achieved, stosstherapy was administered due to concerns over treatment compliance. The patient received 100,000 IU of vitamin D_2 mixed with applesauce (2 capsules of 50,000 IU ergocalciferol) every 2 hours, for a total of 600,000 IU. Daily calcium levels were followed and remained normal. He was discharged home on hospital day 6.

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Table 1. Biochemical Parameters in the Case Patient Before and After Stosstherapy

Laboratory Test	Normal Range	At Diagnosis	Hospital Day 3*	One-Week Follow-up	Two-Week Follow-up	Two-Month Follow-up	Four-Month Follow-up
Alkaline phosphatase (U/L)	< 461	3949	4227	3245	1648	352	267
Calcium (mg/dL)	8.5–10.5	4.9	7.1	9.3	9.3	10.1	10.7
Ionized calcium (mg/dL)	4–4.6	3.12	N/A	N/A	N/A	N/A	N/A
Parathyroid hormone (pg/mL)	10–65	304.9	N/A	N/A	119.7	66.9	51
Phosphorus (mg/dL)	4.5–6.7	3.4	2.9	4.2	4.5	6.2	N/A
1,25-Dihydroxyvitamin D (pg/mL)	27–71	30	N/A	N/A	480	188	75
25-Hydroxyvitamin D (ng/mL)	10–68	10.2	N/A	N/A	31.3	12.4	34

N/A = not available.

*Stosstherapy administered on day 3 of hospitalization.

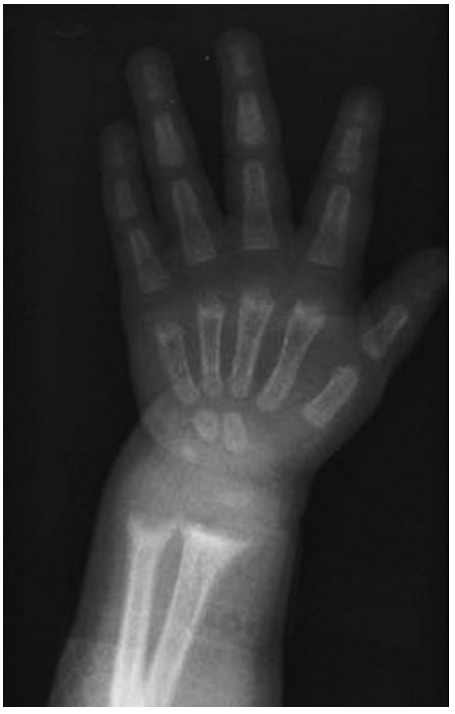

Figure 1. Radiography revealed fraying and cupping of the case patient's radius and ulna, which is indicative of rickets.

Follow-up

Close follow-up was performed at an endocrinology clinic. Biochemical parameters at diagnosis and in subsequent follow-up visits are presented in Table 1. Two months after stosstherapy was initiated, biochemical parameters and the metaphyseal fraying improved. There was complete resolution of radiologic findings (**Figure 2**) as well as biochemical parameters of rickets after 4 months of stosstherapy (Table 1). No adverse events, such as hypercalcemia, were noted.

DISCUSSION

Nutritional rickets remains prevalent among children in the United States. The diagnosis of nutritional rickets in this patient was confirmed by the low serum 25-hydroxyvitamin D (calcidiol) level and by a therapeutic response to stosstherapy as evidenced by (1) a rise in serum phosphorus levels 1 week after stosstherapy, (2) an increase in serum calcium levels, (3) radiographic evidence of mineralization at the zone of provisional calcification of the metaphyses, and (4) a gradual decline in the serum alkaline phosphatase level (Table 1). In the New York area, the mean total serum 25-hydroxyvitamin D values for normal children were 27.5 ± 6.5 ng/mL,[1] a value that was reached in our patient 2 weeks after treatment.

The most common cause of rickets in infants is vitamin D deficiency resulting from exclusive breastfeeding without vitamin D supplementation.[2,3] Human milk typically contains a vitamin D concentration of 25 IU/L or less. The American Academy of Pediatrics recommends that all infants, including those who are exclusively breastfed, have a minimum daily intake of 200 IU of vitamin D beginning during the first 2 months of life.[4]

Treatment Options for Nutritional Rickets

Various regimens for treating vitamin D deficiency rickets have been advocated (**Table 2**)[5–8]; vitamin D_2 administered in doses between 1000 and 2000 IU/day

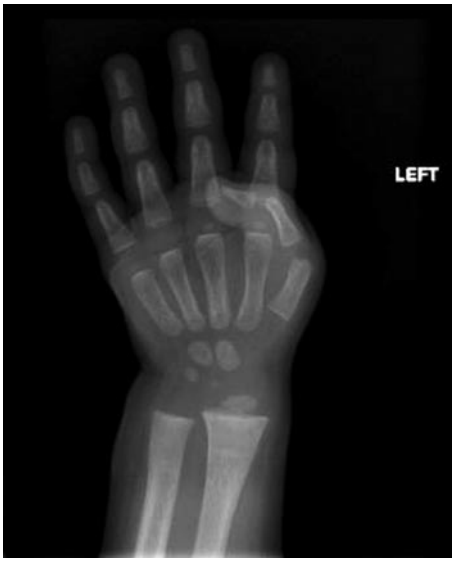

Figure 2. Four months after stosstherapy with vitamin D_2, radiography demonstrated that the fraying and cupping of the patient's radius and ulna had resolved.

(5–10 times the recommended daily allowance) is the most widely used form of treatment.[5] Treatment failures, however, may occur due to poor compliance with this regimen. Therefore, some investigators have advocated vitamin D_2 stosstherapy.[6,7]

Stosstherapy is a term used to describe the administration of a treatment in a very large, single dose instead of the usual series of smaller doses. This treatment method, which is most commonly used in Europe, appears in various contexts, ranging from replacing nutrients to chemotherapy.[9–12] Stosstherapy has been used for the treatment and prophylaxis of vitamin D deficiency rickets since the 1930s.[13] This treatment approach is used because vitamin D is efficiently stored in adipose tissue and muscles. With a larger dose given in a single day, continued conversion to the active metabolite (1,25-dihydroxyvitamin D [calcitriol]) occurs for many weeks and sustains healing of rickets,[6] thereby avoiding the potential damage done by noncompliance with treatment.

Several studies have evaluated the use of stosstherapy in patients with vitamin D deficiency rickets. Shah and Finberg[6] administered 600,000 IU of vitamin D as a single dose in 42 patients over a 10-year period (*see* **Table 3** for treatment protocol), which led to a quick treatment response and complete resolution of the symptoms and radiologic findings of rickets. No adverse reactions (eg, hypercalcemia) were observed in this study, although 3 patients required a second course of vitamin D. A Turkish study by Cesur et al,[7] compared

Table 2. Regimens for Vitamin D_2 Replacement Therapy for Nutritional Rickets

Standard dosing
(A) Administer 1000–2000 IU of vitamin D_2 orally per day until radiographic improvement is seen, then switch to 400 IU per day[5]
(B) Administer 8000–16,000 IU of vitamin D_2 orally per day until radiographic resolution, then switch to 400 IU per day[5]
Stosstherapy
(C) Administer 600,000 IU of vitamin D_2 orally in 6 doses (100,000 IU/dose) every 2 hours over a 12-hr period, followed by supplemental vitamin D_2 (400 IU/day) to start 3 months after stosstherapy[6]
(D) Administer 150,000–300,000 orally as a single dose[7]
(E) Administer 600,000 IU intramuscularly as a single dose, then 400 IU per day[8]

Data from Levine and Carpenter,[5] Shah and Finberg,[6] Cesur et al,[7] and Lubani et al.[8]

Table 3. Stosstherapy Protocol for Vitamin D_2 Replacement in Nutritional Rickets

Two vitamin D_2 capsules (50,000 IU/capsule) are administered every 2 hours over a 12-hour period
Soften the vitamin D_2 capsules by soaking them in a small amount of water
Administer intact capsules with blended food (eg, applesauce)
Ensure total daily calcium intake is 1000 mg/day, either from dietary source or calcium supplementation
Therapy with supplemental vitamin D_2 400 IU/day is begun 3 months after stosstherapy

Data from Shah BR, Finberg L. Single-day therapy for nutritional vitamin D-deficiency rickets: a preferred method. J Pediatr 1994;125:487–90.

the effects of administering 150,000, 300,000, and 600,000 IU of vitamin D in 56 infants and toddlers with nutritional vitamin D rickets. The authors reported resolution of the disease process with all 3 doses, but 6 patients in the 600,000 IU–dose group and 2 patients in the 300,000 IU–dose group developed hypercalcemia, although none of these patients had symptoms of hypercalcemia. Therefore, the authors suggested that administering 150,000 IU of vitamin D might be sufficient to treat rickets. Oliveri et al[14] administered 150,000 IU of vitamin D prophylaxis in early fall to 79 clinically healthy children. This study demonstrated that this dose of vitamin D_2 maintained appropriate levels of 25-hydroxyvitamin D during winter without inducing hypercalcemia or hypercalciuria. A 600,000 IU vitamin D_2 regimen was used in the patient presented here because of our institution's experience using this regimen.[6]

CONCLUSION

We presented this case to illustrate an alternative option for treating patients with vitamin D deficiency rickets. In select pediatric patients with rickets, stosstherapy dosing can be safely used to replace vitamin D. Physicians need to be aware of the available options of nutrient replacement as well as associated difficulties involving regimen compliance and occasional shortages of vitamin D preparations. **HP**

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