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Status epilepticus secondary to hypocalcemia due to vitamin D deficiency

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ABSTRACT

Vitamin D deficiency is becoming more common around the world, owing to reduced sunshine exposure and an imbalanced diet. However, severe hypocalcemia as a result of vitamin D insufficiency is a rare occurrence, and it seldom leads to seizures in children. We present such a case in a 6-month-old infant who presented status epilepticus secondary to hypocalcemia due to vitamin D deficiency, which was first misdiagnosed as epilepsy. Thereby we want to emphasize that hypocalcemia secondary to vitamin D deficiency can lead to convulsion and the importance of vitamin D supplementation.

Keywords: epilepsy; hypocalcemia; anti-epileptic drug

INTRODUCTION

Seizures can be caused by various transient conditions that promote neuronal excitement, including central nervous system infections, fever, electrolyte imbalances, intracranial hemorrhage, and head trauma, in addition to being the most common symptom of epilepsy [1]. Hypocalcemia is one of the electrolyte disturbances that can cause seizures. In addition, vitamin D and parathyroid hormone [PTH) serve a crucial role in maintaining a steady extracellular ionized calcium concentration, which is essential for optimal brain cell function [2]. Vitamin D deficiency is becoming more common around the world, especially in developing countries, owing to reduced sunshine exposure and an imbalanced diet. Vitamin D insufficiency reduces calcium absorption from the intestine, which can result in hypocalcemia. Vitamin D insufficiency causes hypocalcemia, which is most common during periods of rapid growth, such as infancy and adolescence [3]. We report this case to emphasize that hypocalcemia due to nutritional vitamin D deficiency can cause seizures in children and underline the significance of supplementing with vitamin D.

CASE PRESENTATION

A 3- month- old girl was brought to the emergency department after having had symptoms of a seizure at home. The seizure was described as a general tonic-clonic seizure with an upward rotation of the eyes and rhythmic contractions in both her arms and legs. The episode lasted around 2 minutes, according to her mother, and she recovered spontaneously. Her mother also reported that she had a low-grade fever, poor feeding, and vomiting after feeding 2-3 times a day for 5 days and had not received any treatment. She had no significant medical history of seizures, trauma, drug allergy, or any other illness. The patient was 9th -born-child of a 41-years-old mother, had been a fullterm baby (3kg at birth), was born by normal vaginal delivery, and had been exclusively breastfed. The previous history of psychomotor development was completely normal. Her third-elder-brother (11 years old) was

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diagnosed with epilepsy 8 years ago. When we were initial evaluating in the emergency department, the patient had continuous generalized tonic-clonic seizure activity and was unresponded with benzodiazepine. Then, the epilepticus status was effectively controlled with midazolam continuous infusion (0,1 mg/kg/h). A physical examination showed the infant was postictal, her skin and mucous membranes were pale, no meningeal signs, a non-bulging anterior fontanelle, and no skeletal deformities. An abdominal check, as well as examinations of her head, wrists, and legs, all came back normal, and no organomegaly was seen. There was no rachitic rosary on her chest. Her neurological examination was negative for Chvostek and Trousseau signs. The patient's temperature was 38.1°C, her body weight was 5 kg (15th percentile).

In view of the history and clinical features, she was first diagnosed with meningitis with status epileptics. CT of the head originally done without contrast did not suggest any infarction, hemorrhage, or mass effect. Then, lumbar puncture was performed, cerebrospinal fluid (CSF) analysis showed a normal white blood cell count, normal proteins (0.32 g/L), and normal sugar levels (2.84 mmol/L). Other laboratory evaluation in PICU revealed the following: leukocytes 7,800/mm3, hemoglobin 10.7 g/dL, hematocrit 32.0%, platelets 270,000/mm3, C-reactive protein 2.4 mg/L, Natri 138 mmol/L, Kali 4,75 mmol/L, Clo 109 mmol/L, glucose 3,3 mmol/l; International Normalized Ratio (INR) and Prothrombin Time (PT) were normal. With that CSF result and family history, they focused on epilepsy treatment. During the following days in PICU, she was occasionally affected by continuous semi-rhythmic jerks of right face, shoulder and arm; which made them adjusted the midazolam dose (0,3 mg/kg/h) and use valproate acid to control the partial seizure.

Three days later, the patient was admitted to our Neurological Unit. We did a routine biochemical examination to exclude the diagnosis of congenital metabolic disorder and electrolyte disorder (Laboratory data are shown in Table 1); we noted a ionized calcium serum level of 0.63 mmol/L (normal range 1.0–1.32 mmol/L), the serum Ca level corrected for serum albumin was 7.56 mg/dL (1.89 mmol/l); (normal range 2.1–2.5 mmol/L), indicating true hypocalcemia, not pseudo-hypocalcemia. Although serum magnesium levels were modestly low (0.53 mmol/L), there was no evidence of significant hypomagnesemia causing impaired PTH secretion. Furthermore, the serum intact PTH level at the time of admission was extremely high. As a result, we assumed the parathyroid gland was normally functioning because intact PTH increased in response to hypocalcemia. Vitamin D-related disease is the most common cause of hypocalcemia with high parathyroid hormone (PTH) blood concentrations. This led to decrease Ca absorption from the gastrointestinal tract. Another mechanism of hypocalcemia was increased urinary Ca excretion. However, fractional excretion of Ca was remarkably low (0.94mmol/L), indicating Ca resorption enhancement across renal tubules.

Shortly after a definite diagnosis was made, an intravenous infusion of calcium gluconate was started. We also used oral calcium carbonate (250 mg elemental calcium) and vitamin D supplementation (oral calcitriol 0.25 μg daily). Her serial calcium levels started showing an increasing trend and got normalized by day 4 of admission. The seizures did not recur throughout the period of hospitalization, and the infant was discharged home on day 12 of admission with instructions for increased exposure to sunlight and oral calcium with vitamin D3 (250 mg/400 IU once daily), calcitriol (0.25 μg daily)

TABLE 1. Patient's laboratory data on neurological unit

Laboratory investigation	Results	Reference Range
Serum biochemistry		
Albumin	23 g/L	
BUN	0.7 mmol/L	
Creatinine	31.72 micromol/L	
Aspartate aminotransferase	79 U/L	
Alanine aminotransferase	75 U/L	
NH3	86 micromol/L	
Lactate	2.2 mmol/L	
Ca^{2+}	0.63 mmol/L	1.0-1.32 mmol/L
Calcium	1.55 mmol/L	2.1-2.5 mmol/L
Magnesium	0.53 mmol/L	0,66-1.07 mmol/L
Endocrinology		
PTH	327.3 pg/mL	15-65 pg/mL
25-hydroxyvitamin D	4.3 ng/mL	30-40 ng/ml
Arterial blood gas		
pH	7.407	
PaO_2	81.1	
$PaCO_2$	32.0	
HCO_3^-	19.8	
Urinary biochemistry		
Ceton	Negative	
Urinary calcium	0.94 mmol/L	
Urinary creatinine	2725 micromol/L	
Abbreviations: Ca2+, ionized calcium; HCO3-, hydrogen carbonate; PaCO2, partial pressure of arterial carbon dioxide; PaO2, partial pressure of arterial oxygen; PTH, parathyroid hormone		

DISSCUSION

Hypocalcemia may be associated with a spectrum of clinical manifestations, ranging from few symptoms if the hypocalcemia is mild to life-threatening seizures, refractory heart failure, or laryngo-

spasm if it is severe. Calcium homeostasis is maintained by the coordinated actions of PTH and vitamin D. PTH stimulates calcium resorption from the renal tubules and release calcium from the bones. PTH also stimulates the renal production of 1,25(OH)2D from 25-hydroxycholecalciferol (25[OH] D). Sunlight-dependent cutaneous synthesis is the major mechanism for absorption of vitamin D in humans. 1,25(OH)2D is the active form of vitamin D and promotes calcium absorption from the small intestine. Thus, the etiology of hypocalcemia can be related to failure of a component of this system, such as deficiency of or resistance to parathyroid hormone (PTH) or vitamin D, or a defect of the calcium-sensing receptor (CaSR) [4].

Vitamin D deficiency is the most common cause of hypocalcemia. In vitamin D deficiency, low ionized calcium levels stimulate PTH secretion, which increases calcium and phosphorus release from the bone to maintain normal serum calcium levels. Higher PTH levels increase calcium reabsorption in the renal tubules and also cause phosphorus loss in the urine. Therefore, reduced levels of phosphorus and calcium result in decreased bone mineralization. The most common causes of nutritional vitamin D deficiency are prolonged breastfeeding, inadequate consumption of milk products, and avoidance of sun exposure. In our patient, serum levels of PTH were elevated and fractional excretion of Ca was very low, indicating that the parathyroid gland was functioning normally in response to the hypocalcemia, and that the kidneys were acting to enhance tubular Ca reabsorption. Importantly, serum 25-hydroxyvitamin D level was extremely low, indicating that 25-hydroxyvitamin D deficiency was the primary cause of the hypocalcemia in our patient and that all other changes in the serum and urine mineral markers were secondary. Factors affecting the low serum 25-hydroxyvitamin D level might have been that our patient was exclusively breastfed, vitamin D supplementation was not provided, and had less opportunity for sunlight exposure (lying-in darkroom with mother in first 100 days). She was 9th -born-child of 41-years-old, due to the lack of economic conditions, nutrition during pregnancy and postpartum was not guaranteed, so the quality of breast milk could be reduced.

In our case, vitamin D deficiency was probably a chronic condition. We thought that there must have been some factors that triggered hypocalcemia-induced seizure, possibly due to gastroenteritis (fever, vomit, poor feeding). It is plausible that his excitability of the motor area was enhanced by superimposing metabolic factors such as infection-related fever on the vulnerable cerebral cortex, ultimately leading to the seizure episodes. One point to discuss was that our patient had hypocalcemia with no other symptoms except convulsions. Hypocalcemia can cause seizures without concomitant tetany because low ionized Ca concentrations in the cerebrospinal fluid are associated with increased excitability in the central nervous system [5,6].

Vitamin D deficiency is frequent in children with dark skin pigmentation and those who are exclusively breastfed beyond the age of three to six months, especially if other risk factors exist, such as maternal vitamin D deficiency during pregnancy or preterm. Vitamin D deficiency is especially frequent among older children with dark skin pigmentation, those who consume a diet low in vitamin D-fortified foods (for example, a vegan or atypical diet), those who take anticonvulsant or antiretroviral drugs, and those who have malabsorptive diseases or obesity. Residence at higher latitudes, the winter season, and other causes of inadequate sun exposure are also risk factors [4,7].

Exclusive breastfeeding is a significant risk factor for vitamin D deficiency and rickets. Even in a vitamin D-deficient mother, the vitamin D level of breast milk is low (15 to 50 international units/L [0.4 to 1.2 micrograms/L]). Exclusively breastfed infants consuming an average of 750 mL of breast milk daily ingest only 10 to 40 international units/day (0.25 to 1 microgram/day) of vitamin D in the absence of sun exposure or supplement use [8-10]. For most infants, exposure to sunlight is generally not a sufficient source of vitamin D. One study that included Black and White infants estimates that most breastfed infants need to be exposed to sunlight for at least 30 minutes/week while wearing only a diaper in order to maintain 25OHD concentrations at >20 ng/mL (50 nmol/L) [11]. This amount of sun exposure is unlikely given more current recommendations to limit sun exposure in infants younger than six months old. As a result, starting a few days after delivery, all exclusively breastfed newborns should get 400 international units (10 micrograms) of vitamin D supplements daily [8,12,13].

For infants and toddlers aged 0–1 year who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 weeks to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 400-1000 IU/d [14]. Hypocalcemic seizures should be treated with intravenous calcium. Calcium gluconate is favored over calcium chloride because it is less irritating and has a lower risk of causing tissue necrosis if it extravasates.

CONCLUSION

Electrolyte abnormalities such as hypocalcemia should be considered when investigating the first

seizures in non-epileptic children. Exclusively breastfed infants of mothers with inadequate exposure to sunlight are at high risk for nutritional rickets and should start vitamin D supplementation soon after birth.

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