CASE REPORT

Seizures in an Infant on Anti-Tuberculosis Agents

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ABSTRACT

A two-month-old baby boy on prophylaxis anti-tuberculosis (anti-TB) since the age of two weeks presented with several episodes of seizures. He was afebrile and metaphyseal widening of both lower and upper limbs were noted on clinical examination. Laboratory investigations revealed hypocalcaemia, elevated alkaline phosphatase (ALP) and vitamin D deficiency. This case report discusses the possible causes of vitamin D deficiency in a child and highlights that although exclusive breastfeeding and limited sun exposure are the main cause of vitamin D deficiency, other risk factors need to be considered.

Keywords: Hypocalcemia, Vitamin D deficiency, Anti-tuberculosis, Seizures, Infant

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INTRODUCTION

Vitamin D is an important steroid hormone for calcium and phosphate homeostasis. Vitamin D deficiency results in failure of bone mineralisation leading to the development of rickets in children. Hypocalcaemia may be the first manifestation of vitamin D deficiency in young infants, which may be severe enough to cause seizures (1). Exclusive breastfeeding and maternal vitamin D deficiency are among the established risk factors for vitamin D deficiency in infants (1). Nevertheless, other risk factors should be considered.

CASE REPORT

A two-month-old male developed three episodes of seizures while attending a hospital follow up. He had both upper and lower limbs myoclonic jerk and twitching of the left eye. The first two episodes of seizures aborted spontaneously, while the third, following intravenous midazolam (0.1 mg/kg). Immediate investigations revealed metabolic acidosis, severe hypocalcaemia with ionised calcium of 0.74 (1.10-1.35 mmol/L) and capillary blood glucose of 5.6 (2.2-5.0 mmol/L). Intravenous calcium gluconate 10% infusion over ten minutes and intravenous infusion of phenobarbitone 20 mg/kg over 20 minutes were commenced. There was a history of spontaneously aborted seizure at home a day before the hospital visit. There was no history of vomiting, irritability, fever or trauma.

The baby was delivered at 37 weeks via an emergency lower segment caesarean section for foetal distress. He was born to non-consanguineous parents and was the only child. There was no family history of metabolic or congenital diseases. His medication includes syrup Isoniazid 35 mg daily and syrup Pyridoxine 5 mg daily. It was commenced at the age of two weeks as the mother had pulmonary tuberculosis (PTB) reactivation complicated by pleural effusion at 27 weeks of gestation. All his tuberculosis workup, including gastric lavage for acid-fast bacilli (AFB), *Mycobacterium tuberculosis* culture and sensitivity, as well as placental histopathological examinations, were negative for tuberculosis. He was formula fed till the age of two weeks but was later fully breastfed following the mother's negative sputum AFB smear.

Post-seizure examination revealed an active afebrile infant with normal vital signs. There was metaphyseal widening of both lower and upper limbs, but no rachitic rosary, chest deformity, or frontal bossing noted. His weight (3.6 kg) and height (54 cm) were below the 3rd percentile for age and gender. There were no signs of meningism, and other systemic examinations were unremarkable.

A repeat serum calcium showed a value of 1.42 (2.25-2.75 mmol/L). He was commenced on a 4-hourly calcium infusion with close cardiac monitoring. Other abnormal investigation results included raised alkaline phosphatase (ALP), raised parathyroid hormone (PTH), low phosphate and low 25-hydroxy vitamin D [25(OH) D]. The laboratory investigations results performed throughout his five days of hospitalisation are listed in table I. He developed no subsequent seizures during the

Table I: Laboratory investigation results during hospital admission

Parameters	Day 1			Day 2-Day 5	Day 6	Reference Interval
	1430 hr	1600 hr	2230 hr			
Adjusted calcium, (mmol/L)	1.30	1.46	2.45	1.72-2.30	2.28	2.25-2.75
Ionised calcium, (mmol/L)	0.74					1.10-1.35
Magnesium, (mmol/L)	0.79	0.79	0.75	0.74-0.89	0.80	0.62-0.91
Phosphate, (mmol/L)	1.54	1.53	1.28	1.08 – 1.26	1.05	1.15-2.15
Sodium, (mmol/L)	139					136-145
Potassium, (mmol/L)	4.2					3.50-4.50
Chloride, (mmol/L)	107					97-107
Urea, (mmol/L)	1.10					3.20-8.10
Creatinine, (µmol/L)	16					14-34
Total protein, (g/L)	56					64-83
Albumin, (g/L)	39	38	36	34 – 39	38	38-54
ALP, (U/L)	1483		1432	1294 - 1473	1433	<449
ALT, (U/L)	35					<41
AST, (U/L)	28					<32
Total bilirubin, (µmol/L)	15					<17
PTH, (pmol/L)	16.57			13.47		1.58-6.03
25(OH)D, (nmol/L)					9.18	Deficient:<25 Insufficient:25-75 Sufficient:76-250

hospitalisation and was discharged with oral calcium carbonate, cholecalciferol and 1-alphacalcidol. The serum calcium repeated two weeks later during follow up was normal whilst ALP finally normalised after two months of treatment.

DISCUSSION

Hypocalcaemia was the most apparent cause of seizure in this infant. Causes of hypocalcaemia with secondary hyperparathyroidism include vitamin D deficiency, resistance to PTH action, inherited mutation to vitamin D receptor and mutation of 1-ά-hydroxylase enzyme. The low 25(OH)D, raised ALP, hypophosphataemia and raised PTH pointed to vitamin D deficiency as a cause of symptomatic hypocalcaemia in this infant. In vitamin D deficiency, intestinal absorption of calcium and phosphate is decreased. In response to hypocalcaemia, PTH secretion is triggered. PTH liberates calcium from bone and increases calcium absorption from kidneys, while the phosphaturic effect of PTH causes hypophosphataemia.

The prevalence of vitamin D deficiency among six-month-old infants was 13%, which is lower than the 90% prevalence reported in cord blood samples, based on a recently reported study in Indonesia (2). Hypocalcaemia symptoms such as seizures, tetany and paraesthesia may be the first presentation of vitamin D deficiency in infants less than six months of age (1). The annual incidence of hypocalcaemic seizures secondary to vitamin D deficiency was estimated to be 3.49 per million children aged 0–15 years (95% CI: 2.81–4.26) (3). Children may also present soon after weight-bearing age with various skeletal deformities such as rickety rosary of the costochondral junctions and bowing of the legs (1). Pathological fractures may occur in severe cases.

The cause of vitamin D deficiency in children may be multifactorial, as demonstrated in this case. Vitamin D is derived from cutaneous synthesis and dietary intake of food containing vitamin D. Infants at higher risk of developing vitamin D deficiency are those with dark-pigmented skin tone, chronic illness, inadequate nutrition, and exclusive breastfeeding (1). Since the age of two weeks, being exclusively breastfed in a mother who was most likely to be vitamin D deficient is a major contributing factor in this infant. Although the mother's serum 25(OH)D was never measured, she had several risk factors such as tuberculosis, on anti-TB medication, limited sunlight exposure and not on any vitamin D supplements. The normal renal profile and liver enzymes in this infant excluded liver and kidney diseases as a cause of his vitamin D deficiency.

In adults, vitamin D deficiency is a well-recognised complication of anti-TB (4), but in children, the reports have been limited and certainly not as young as in this case. Rifampicin and isoniazid significantly reduce vitamin D2 and D3 levels (4). Isoniazid impairs the activity of hepatic 25-hydroxylase and possibly renal 1α-hydroxylase (4). On the other hand, rifampicin increases clearance of 25(OH)D by inducing hepatic

cytochrome p450 enzyme (5).

Vitamin D deficiency following treatment with both isoniazid and/or rifampicin does not usually result in symptomatic hypocalcaemia unless in those already at increased risk of vitamin D deficiency. There are several reports of symptomatic hypocalcaemia because of anti-TB in children (4,5). All shared the same biochemical findings of hypocalcaemia, secondary hyperparathyroidism, elevated serum ALP and vitamin D deficiency. Recognising that anti-TB agents may precipitate clinically significant hypocalcaemia is essential to ensure adequate vitamin D supplementation.

Fortunately, the effects of anti-TB on vitamin D metabolism are often reversible (4). In this infant, calcium and vitamin D supplementation resulted in normalisation of serum 25(OH)D, calcium and ALP level. Monitoring of vitamin D level and other bone parameters such as ALP and PTH following cessation of anti-TB therapy is warranted, more so when vitamin D deficiency complicates treatment.

CONCLUSION

Symptomatic hypocalcaemia may be the first manifestation of vitamin D deficiency in infants. The cause of vitamin D deficiency in children may be multifactorial and the risk factors need to be identified.

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