Congenital hypoparathyroidism misdiagnosed as infantile seizure

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Introduction

Seizures in neonates are relatively common and often encountered by general practitioners. Their presence may be the first sign of neurologic dysfunction, and they are powerful predictors of long-term cognitive and developmental impairment.1 Patients are often labeled as cryptogenic or idiopathic epilepsy, and in some cases, appropriate investigations to assess for provoking factors and/or treatable causes are overlooked.

Hypocalcaemia is a common cause of seizures in children and its serum concentration is maintained within a narrow physiological range by complex controlling mechanisms. The most prominent mechanisms are; Parathyroid Hormone (PTH), active vitamin D (1,25-(OH)2 D), and Calcium Sensor Receptors (CaSRs) acting in renal, intestinal, parathyroid, and bone tissues to maintain the calcium homeostasis. Failure of any of these homeostatic mechanisms or inadequate compensation hypocalcaemia occurs.2 Hypoparathyroidism can be acquired, inherited, or idiopathic, and is caused by inability to synthesize or secrete PTH, abnormal parathyroid gland development, destruction of parathyroid tissue or resistance of circulating PTH (pseudohypoparathyroidism).2

Case Report

A 3-months-old infant was referred to our endocrine unit with recurrent seizures, body stiffness, noisy breathing and bilateral cataract. He was previously been diagnosed as epilepsy in a syndromic child. Biochemical investigation revealed hypoparathyroidism, brain MRI was suggestive of decrease myelination for age, EEG revealed normal study, and a diagnosis of congenital hypoparathyroidism was confirmed. After calcium and vitamin D replacement, the infant improved and was seizure free off antiepileptic therapy. This case therefore explores an unusual case of seizure disorder. It further highlights the fact that not all epilepsies are cryptogenic or genetic epilepsy, therefore treatable acute symptomatic etiologies should be adequately searched.

Abstract

The occurrence of seizure in children is a common neurologic dysfunction and finding the underlying aetiology is critically important as it determines the prognosis and outcome of the seizure and also guides therapeutic strategies. Parathyroid hormone (PTH) plays key role in the complex controlling mechanisms regulating calcium and phosphate balance. An insufficient circulating PTH level is a common cause of hypocalcaemia. A 3-months-old infant was referred to our endocrine unit with recurrent seizures, body stiffness, noisy breathing and bilateral cataract. He was previously been diagnosed as epilepsy in a syndromic child. Biochemical investigation revealed hypoparathyroidism, brain MRI was suggestive of decrease myelination for age, EEG revealed normal study, and a diagnosis of congenital hypoparathyroidism was confirmed. After calcium and vitamin D replacement, the infant improved and was seizure free off antiepileptic therapy. This case therefore explores an unusual case of seizure disorder. It further highlights the fact that not all epilepsies are cryptogenic or genetic epilepsy, therefore treatable acute symptomatic etiologies should be adequately searched.

Conception of seizure in children is a common neurologic dysfunction and finding the underlying aetiology is critically important as it determines the prognosis and outcome of the seizure and also guides therapeutic strategies. Parathyroid hormone (PTH) plays key role in the complex controlling mechanisms regulating calcium and phosphate balance. An insufficient circulating PTH level is a common cause of hypocalcaemia. A 3-months-old infant was referred to our endocrine unit with recurrent seizures, body stiffness, noisy breathing and bilateral cataract. He was previously been diagnosed as epilepsy in a syndromic child. Biochemical investigation revealed hypoparathyroidism, brain MRI was suggestive of decrease myelination for age, EEG revealed normal study, and a diagnosis of congenital hypoparathyroidism was confirmed. After calcium and vitamin D replacement, the infant improved and was seizure free off antiepileptic therapy. This case therefore explores an unusual case of seizure disorder. It further highlights the fact that not all epilepsies are cryptogenic or genetic epilepsy, therefore treatable acute symptomatic etiologies should be adequately searched.

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hydroxy vitamin-D 95.28 nmol/L (75-185), TSH – 6.0 µU/mL (0.7-6.4), free T4 1.50 ng/dL (0.8-2.0), random blood sugar (RBS) 90 mg/dL. Urea, electrolytes, creatinine (U/E/Cr) and Complete Blood Count (CBC) were essentially normal. Serum parathyroid hormone (PTH) was 10.6 pg/mL (14-72 pg/mL), confirming a diagnosis of hypoparathyroidism. Genetic panel for exome sequencing for pathogenic gene variations was sought, and the result showed no pathogenic or possibility of pathogenic variations to be the cause of the clinical symptoms detected. Brain-magnetic resonance imaging (MRI) revealed generalized hypomyelination in both cerebral hemispheres (Figure 1), abdominal scan and Brain-electroencephalogram (Figures 2 and 3) revealed normal studies.

**Discussion**

A neonate presenting with definite new onset seizures, investigations for any provocative factors that may cause the seizures are recommended. There are many possible reasons for neonatal seizures, and careful and thorough history can give a clue to the most likely cause in most situations. Neonatal seizures can be from Hypoxic-Ischemic Encephalopathy (HIE), intracranial haemorrhage, metabolic disorders like hypoglycemia, hypocalcaemia, hypomagnesaemia and others such as inborn errors of metabolism. Other causes are genetic disorders due to genetic mutations, intracranial infections, malformation syndromes and benign neonatal seizure syndromes.

Our patient started having seizures from third day of life with no associated history of fever at the onset to suggest possibility of infections, or adverse perinatal events to suggest possible HIE or intracranial haemorrhage. Furthermore, there was no family history of seizures to suggest benign familial neonatal seizures. However, there may be possibility of genetic disorders because of history of consanguinity in the family. In addition, metabolic disorders could also be likely, because these are common causes of neonatal seizures in the absence of fever or adverse perinatal events, and they tend to commonly cause symptoms from the third day of life. Therefore, when this patient presented at the age of two weeks with history of increased seizures, meningitis should not have been the most likely cause of the seizures. Other common possibilities should have been considered like metabolic disorders. Therefore we thought hypocalcaemia secondary to hypoparathyroidism is the cause of seizures in this patient because of the repeated low serum calcium and low PTH. According to International League Against Epilepsy (ILAE), to attribute a seizure to an electrolyte abnormality, the biochemical derangement should be detected within 24 hours of the seizure. Hypocalcemic-related seizures depend on the rate of decrease in serum calcium and degree of hypocalcemia. The resultant hypocalcaemia results in increased neuronal excitability due to reduced extracellular concentration of calcium rather than depleted intracellular levels and both generalised tonic-clonic or focal seizures can occur with hypocalcaemia. The finding in this report is similar to what was reported by Mine et al in Turkey who reported an infant with...
similar presentation due to hypoparathyroidism. Kunstadter et al. also reported two neonates with idiopathic hypoparathyroidism with repeated seizures. Furthermore, in South Africa, Seedat et al. reported a case of acute symptomatic seizures in an adult, which are caused by idiopathic hypoparathyroidism other than epilepsy.

Hypoparathyroidism can be acquired, inherited, or idiopathic, and is caused by inability to synthesize or secrete PTH, abnormal parathyroid gland development, destruction of parathyroid tissue, peripheral resistance to PTH, or due to genetic disorder causing activating mutations in the CaSR.

Other possible diagnoses considered in this child were early infantile onset heredodegenerative disease, mitochondrial cytopathy, hypomyelinating leukodystrophy, peroxisomal disorder, Kearns-Sayre syndrome, neurotransmitter defect or Pelizaeus-Merzbacher. But the genetic study did not show any pathogenic or likely pathogenic variations to be causative of the clinical symptoms detected. However, genetic tests may not always give a definitive answer, in some cases, testing may not identify a genetic variant even though one exists. This may be due to limitations in current medical knowledge or testing technology. Accordingly, variants in regions of insufficient coverage may not be identified and/or interpreted. Therefore, it is possible that pathogenic variants are present in one or more of the genes analysed, but have not been detected. The patient was therefore diagnosed as idiopathic hypoparathyroidism with neurologic sequelae (spastic quadriplegia, visual and hearing impairment).

Child was managed with oral calcium and calcitriol (vitamin D₃) for the hypoparathyroidism. It is recommended to use oral calcium and vitamin D supplementation as therapy for hypoparathyroidism, but serum calcium should be maintained in the lower range of normal to avoid hypercalciuria and resultant nephrolithiasis. Anticonvulsants are used for seizures control in hypoparathyroidism, commonly used agents are phenytoin, valproate, carbamazepine, and levetiracetam. In this study, anticonvulsant (valproate) was continued for 2 years before it was weaned completely, and the child has enjoyed seizure freedom for 4 years now. Additional supportive management was oral baclofen for spasticity and physiotherapy for delayed motor development. The child had cataract extraction at the age of 18 months and regained full vision. His serum calcium was in the range of 1.7-2.1 mmol/L in the last four clinic visits. So far, he is seizure free, no stridor and has regained full vision and hearing, but is yet to achieve neck control or sit unsupported.

Conclusions

This case highlights the importance of searching for etiology of epilepsy in all cases rather than classifying most epilepsies cryptogenic or genetic as there are many acute symptomatic and some remote symptomatic epilepsies out there that are amenable to treatment like our index case!

References