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Case Report

Thiamine pyrophosphokinase deficiency causes a Leigh Disease like phenotype in a sibling pair: identification through whole exome sequencing and management strategies

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ABSTRACT

We present a sibling pair with Leigh-like disease, progressive hypotonia, regression, and chronic encephalopathy. Whole exome sequencing in the younger sibling demonstrated a homozygous thiamine pyrophosphokinase (TPK) mutation. Initiation of high dose thiamine, niacin, biotin, α-lipoic acid and ketogenic diet in this child demonstrated improvement in neurologic function and re-attainment of previously lost milestones. The diagnosis of TPK deficiency was difficult due to inconsistent biochemical and diagnostic parameters, rapidity of clinical demise and would not have been made in a timely manner without the use of whole exome sequencing. Molecular diagnosis allowed for attempt at dietary modification with cofactor supplementation which resulted in an improved clinical course.

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1. Introduction

Thiamine pyrophosphate (TPP) is a required cofactor for the mitochondrial enzyme complexes pyruvate dehydrogenase, α-ketoacid dehydrogenase, and branched chain ketoacid dehydrogenase. It is also required for the cytosolic transketolase and the peroxisomal α-oxidation of 3-methyl-branched and straight chain 2-hydroxy long chain fatty acids by 2-hydroxyacyl-CoA lyase 1. TPP is synthesized by the enzyme thiamine pyrophosphokinase (TPK) [1–17]. Mayr et al. demonstrated that patients with autosomal recessive mutations in TPK can present with variable degrees of encephalopathy, developmental delay and hypotonia [18]. In their cohort, illness and other causes of increased catabolism triggered acute decompensation. The individuals with TPK mutations had motor dysfunction particularly related to striatal, basal ganglial, and cerebellar regions of the brain, but cognition appeared to remain intact [18]. In the three families previously reported, the range of symptomatic presentation was between 18 months and 4 years. Thiamine supplementation was attempted in three out of five patients. Two of those were reported to have stabilization of symptoms with some improvement in function. One child was placed on a 70% fat containing diet. Laboratory analyses obtained in this cohort noted consistent elevations in α-ketoglutaric acid [18].

2. Case series

Here we describe the clinical presentation and care of a sibling pair, born to consanguineous second-cousins of Chinese descent.

2.1. Patient 1

P1 was born via cesarean section for fetal decelerations at term. Initial developmental delay and hypotonia were noted at 7 months of age with slow developmental progress until 26 months, when she developed a febrile illness and rapidly regressed in both motor and cognitive milestones. At 28 months of age she was admitted to hospital for increasing fatigue, weakness, decreased oral intake, lethargy, and intractable seizures with severe and rapid progression to coma. She died at 29 months secondary to multi-organ failure after having suffered multiple metabolic strokes in the setting of metabolic collapse.

Cerebral MRI at 12 months of age demonstrated T2 bright abnormalities (Fig. 1, A–C) in the basal ganglia and thalami. Repeat MRI during her metabolic collapse at 28 months revealed progressive findings suggestive of mitochondrial disease (Fig. 1, D–F).

Pre- and post-mortem laboratory evaluations were extensive. Cytogenetic, molecular and biochemical analyses included karyotype, mitochondrial DNA mutation and deletion analysis, plasma amino acids, electron transfer analysis via muscle biopsy, pyruvate carboxylase and pyruvate dehydrogenase levels from post mortem fibroblast analyses. All the studies were non-diagnostic. Urine organic acids demonstrated elevations in lactic, α-ketoglutaric and fumaric acids. Thiamine levels were not obtained during her clinical decompensation or post-mortem studies.

2.2. Patient 2

P2 was born at 38 weeks of gestation via repeat cesarean section after an uneventful pregnancy. Initial evaluation at two weeks was without concern as he was breast-feeding well, with normal tone and neurologic exam. By four months, his exam demonstrated mild hypotonia, episodic extremity stiffening and a decreased level of alertness.

By 12 months of age, his hypotonia progressed with inconsistent head control, inability to sit without support, and persistent drooling with poor oral intake. A cranial MRI with sedation was obtained at this time and revealed T2 abnormalities similar to his sibling (Fig. 1, G–I). At 18 months he was admitted to the hospital because neurological decline. His exam was notable for complete loss of head control, bulbar dysfunction, fatigue, weakness, worsening hypotonia, and persistent food refusal except for very small quantities of a traditional Chinese rice porridge. Immediately upon admission, additional biochemical laboratory evaluation was performed, and aggressive management of his fluid and nutritional status was initiated because of his sister's rapid metabolic decompensation prior to her death. Laboratory analyses included interpretations of plasma amino acids, acylcarnitine profile, lactate, pyruvate and very long chain