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Thiamine phosphokinase deficiency and mutation in TPK1 presenting as biotin responsive basal ganglia disease

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ABSTRACT

The product of thiamine phosphokinase is the cofactor for many enzymes, including the dehydrogenases of pyruvate, 2-ketoglutarate and branched chain ketoacids. Its deficiency has recently been described in a small number of patients, some of whom had a Leigh syndrome phenotype. The patient who also had a Leigh phenotype was initially found to have a low concentration of biotin in plasma and massive urinary excretion of biotin. Despite treatment with biotin and thiamine, her disease was progressive. Mutations c.311delG and c.426G > C were found in the TPK1 gene.

1. Introduction

Thiamine phosphokinase (TPK) (EC2.7.6.2) catalyzes the transfer of a pyrophosphate moiety from ATP to thiamine to form thiaminepyrophosphate (TPP). This compound is the cofactor for a variety of enzymes, particularly pyruvate dehydrogenase, 2-ketoglutarate dehydrogenase, and the branched chain ketoacid dehydrogenase, as well as transketolase and 2-hydroxyacylCoA lyase.

Deficiency of TPK activity has only recently been reported in seven patients from five families [1–3]. It is the purpose of this report to describe another patient with this disease.

2. Case report

The patient was 29 years old when she was most recently seen at the University of California San Diego Rady Children's Hospital. She had been observed over a period of more than 20 years. She was said to have had an uneventful 2.5 years of life, except for some ataxia. Then following an acute otitis treated with amoxicillin, she became responsive only to pain and had hyporeflexia of the legs. She was admitted to Children's Hospital Orange County. An EEG was diffusely abnormal, and MRI of the brain showed abnormal high signal in the basal ganglia, and thalamic and dentate nuclei. Nuclear magnetic resonance spectrometry showed necrosis in deep gray matter. Biopsied muscle was histologically normal. Following that illness, she was profoundly deaf.

At 4.5 years of age following a sinus infection and a temperature of 102 °F, she developed nystagmus and became dystonic. This was followed by decreased consciousness, increased tone and posturing. Concentration of pyruvate in the plasma was normal. Lactate ranged from 0.2 to 0.4. mmol/L. A diagnosis of Leigh disease was made, and treatment was initiated with thiamine [4].

At 10 years of age, she had dystonic quadriparesis and was wheelchair bound. She had rotatory nystagmus, optic atrophy and profound hearing loss. Plasma concentration of lactate was normal, but that of pyruvate ranged from 0.11 to 0.19 mmol/L. CSF lactate was 4.7 mmol/L.

At 14 years of age, she was in hospital at St. Joseph's Hospital of Orange County following an acute viral illness. A gastrostomy tube was placed for hydration.

Physical examination at 17 years of age revealed dystonic posturing in a wheelchair. Parents communicated with her by sign language. Respirations were 20 and pulse 110 per min. Blood pressure was 120/85. She had mild nystagmus. Muscle tone was increased and strength normal. Deep tendon reflexes were exaggerated. Plasma concentration of glucose was 4.9, lactate 1.7 and pyruvate 0.14 mmol/L (normal values 3.9–5.5, 0.6–2.3 and 0.08–0.16 respectively).

At 26 years of age, she experienced appreciable regression. She stopped sleeping normally at night, averaging 3–4 h, and began refusing to eat or drink. She had been toilet trained for years and lost this ability. She began retaining urine. She was wheelchair bound and required truncal support. She developed gastroenteric reflux disease and was treated with a fundoplication.

Transaminases were marginally elevated (AST was 54 and ALT 67 U/L; control levels 14–36 and 9–52 respectively). In cerebrospinal fluid, lactate was 4664 and pyruvate 135 (controls 671–2036 and

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0–78 μmol/L respectively). Concentration of alanine in plasma was 532 μmol/L (control 246–486). Plasma acylcarnitines were normal, as were concentrations of carnitine in plasma. Analysis of the gene for SLC19A3 at the Gusella Laboratory at Massachusetts General Hospital was normal. Plasma concentration of biotin was 0 and urinary excretion urine was over 1500 μmol/mol creatinine (control 10–120). Treatment with biotin (120 mg daily) was begun at 9 years of age. She also received carnitine intermittently, and riboflavin.

Mutational analysis (GeneDx, Gaitherberg, MD) revealed 2 mutations in the TPK1 gene: c.311delG, p.104SfsX9, and c.426G > C, p.L142F.

3. Methods

Biotin was assayed in blood and urine by an immunochemical method [5]. Activities of carboxylases were assayed in lymphocytes.

4. Results

Plasma concentrations of pyruvate ranged from 0.14 to −0.19 mmol/L (control 0.8–0.16); those of lactate were repeatedly normal. Carboxylase activity in lymphocytes ranged from 39 to 49% of control (Table 1).

Concentrations of biotin in plasma were undetectable on two occasions (Table 2). Following treatment of 10 mg per day of biotin, plasma concentrations rose appreciably. Urinary excretion of biotin was enormous.

At 10 years of age, treatment was initiated with 10 mg of biotin daily, and the plasma concentration of biotin rose to 25 nmol/L and the urinary excretion to 3658 μmol/molCr. Normal concentrations are 0.3–2.8 nmol/L in plasma and 10-120 μmol/molCr in urine. Renal transport of biotin was tested after 8 days without supplemental biotin. Plasma concentration was 5.4 nmol/L and urinary excretion 324 μmol/molCr. Following an oral dose of 5 μg/kg of biotin, biotin clearance was 249 mL/min; creatinine clearance was 100 mL/min. In a control individual, biotin clearance was 42 mL/min. The patient excreted 43% of administered biotin in 4 h, while the control excreted 26%. Creatinine clearance was normal (Table 3). Clearance of biotin was 294 ml/min, 7 times that of a control individual. The control level was similar to that of 2 normal individuals reported (Table 3).

5. Discussion

Deficiency of TPK was first reported by Mayr, et al., in 2011 [1]. Three patients had episodic ataxia, retardation of psychomotor development and dystonia. One had spasticity and seizures. Another patient [2] had a Leigh-like presentation of global developmental delay, severe truncal hypotonia, and hypertonic limbs with brisk deep tendon reflexes. Another patient [2] had a viral illness at 3 months, which was followed by ataxia and loss of ability to walk. Reflexes were brisk. After recovery, varicella at 32 months was followed by extrapyramidal disease and hypertonia. At 36 months, she developed encephalopathy following gastroenteritis, and required a nasogastric tube for nutrition. Findings on MRI included hyperintense signal in the dentate nucleus, and throughout the basal ganglia in another patient, as well as cortical atrophy [2].

Lactic acidemia has been observed in some patients [1–3], but levels have been normal in others. 2-Ketoglutaric aciduria appears to be a better marker for the disease [1]. It was also observed in siblings reported by Fraser, et al. [5], who had a Leigh-like phenotype.

Treatment with thiamine has been reported to prevent further episodes of encephalopathy [2]. However, no obvious response to treatment has been observed in other patients, including the subject of this report. Doses employed have included 500 mg daily. High doses, up to 3 g for extended time, have had no deleterious effect [6]. Treatment with biotin has also been recommended [6]. High doses up to 3 g for extended time have had no deleterious effects [6]. In our patient, treatment with biotin was continued at 100 mg daily.

The SLC19A3 gene is located on chromosome 7q34–35 and contains nine exons. Mutations previously reported have included c.478C > T (p.Ser160Leu) and c.614G > C (p.Asp222His), both in homozygosity [2,6]. Neither of the mutations found in this family have previously been reported. The c.311delG mutation changes a cystine to a serine at 104, creating a stop codon at position 9 of the new reading frame. It would be predicted to destroy enzyme activity. The L142F mutation is a change in a well-conserved residue, and it was predicted in silico to damage protein structure and function.

The active cofactor for thiamine in animal tissues is TPP. Its synthesis from thiamine is catalyzed by TPK. This takes place in the cytoplasm, where it is available for transketolase. To act as cofactor for the α-ketoacid dehydrogenases, it must be transported to the mitochondrial matrix. This is catalyzed by a TPP transporter in the inner mitochondrial membrane. Defective activity of TPK should affect all enzymes for which it is a cofactor, but major effects appear to be on pyruvate dehydrogenase and 2-ketoglutarate dehydrogenase.

Among disorders of thiamine metabolism in addition to TPK1 deficiency, thiamine responsive megaloblastic anemia (OMIM 249270) resulting from mutations in SLC19A2 and expresses as diabetes mellitus and sensorineural deafness [7]. Biotin or thiamine-responsive basal ganglia disease (OMIM607483) is caused by mutations in SLC19A3 [8]; and symptoms include encephalopathy, coma, seizures, and dystonia, and is the most common of the disorders. Mutations in the thiamine

Table 1

	Lymphocyte carboxylase activity		
	pmol/min/mg/protein		
	PropionylCoA Carboxylase	3-MethylcrotonylCoA Carboxylase	Pyruvate Carboxylase
Patient N.M.	182	82	17
Control	368	211	36

Table 2

	Biotin concentration in blood and urine	
	Plasma	Urine
	nmol/L	μmol/molcreatinine
Patient N.M. pretreatment	0	5
Pretreatment	0	19
Treatment with biotin 10 mg daily	25	3658
	102	5773
Controls	03.2.8	10–120

Table 3

	Clearance of Biotin and Creatinine	
		ml/min
	Biotin	Creatinine
Patient N.M.	294	100
Control	42	
Published Control	39	
Published Control	52	

Biotin treatment was omitted for 8 days prior to study. Patient and control were given a single oral dose of 5 μg/Kg. The patient excreted 43% of administered biotin in 4 h. Over the 24-h period, she excreted 438 μg of biotin; or 267% of the administered dose. A control individual excreted 265.

transporter (mitochondrial thiamine pyrophosphate- ThPP) (SLC25A19) lead to Amish microcephaly (OMIM607196) with lactic and 2-Ketoglutaric aciduria [9]. Mutations in that gene [10] lead to striatal degeneration and polyneuropathy (OMIM613710). In addition, patients with deficiency of the pyruvate dehydrogenase complex (OMIM312170) and maple syrup urine disease (OMIM248600) may also be thiamine responsive [3].

Thiamine transporter (THR2) deficiency, resulting from mutations in the SLC19A3 gene also leads to Leigh syndrome [11]. Treatment with biotin and thiamine has been reported [11] to be effective.

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