Thiamine pyrophosphokinase deficiency due to mutations in the TPK1 gene: a rare, treatable neurodegenerative disorder

Christina Rüsch1, Saskia B. Wortmann2,3, Reka Kovacs-Nagy2,3, Patrice Grethen2, Johannes Häberli5, Bea Latal6, Georg M. Stettner1

1University Children’s Hospital Zurich, Division of Pediatric Neurology, Zürich, Switzerland; 2Technische Universität München, Institute of Human Genetics, München, Germany; 3Hämophilie Zentrum München, Institute of Human Genetics, Neuperlach, Germany; 4Salzburger Landeskliniken (SALK) and Paracelsus Medical University (PMU), Department of Pediatrics, Salzburg, Austria; 5University Children’s Hospital Zurich, Division of Metabolism, Zürich, Switzerland; 6University Children’s Hospital Zurich, Child Development Center, Zürich, Switzerland

Background

Thiamine is an essential nutrient, absorbed in the small intestine. The cytosolic thiamine pyrophosphokinase (TPK) phosphorylates thiamine to the active form thiamine pyrophosphate (TPP). s. Fig.1. TPK acts as a cofactor for the cytosolic transketolase and mitochondrial enzymes involved in the oxidative decarboxylation, as well as for peroxisomal enzymes. A number of defects in the thiamine transport and metabolism are known to cause distinct diseases. In 2011, a severe neurodegenerative, Leigh-like syndrome due to TPK deficiency caused by TPK1 gene mutations was identified.

Case Report

- Psychomotor regression at age 6 and 9 months with loss of previously acquired developmental milestones, muscular hypotonia, atactic movement disorder and encephalopathy triggered by febrile infections.
- Laboratory findings: Slightly elevated serum and CSF lactate, increased α-ketoglutarate in urine organic acids analysis.
- MRI (age 21 months; Fig.2): Bilateral focal T2 hyperintense lesions with diffusion restriction in the basal ganglia, thalamus, dentate nuclei, and centrally in the intraorbital optic nerves.
- MRI (age 35 months; Fig.3): New bilateral lesions within the putamen, regression of the lesions in the caudate and dentate nuclei, stationary posterior periventricular white matter changes.
- Genetic testing: Compound heterozygous, biallelic mutations in the TPK1 gene: c.576T>G; p.Cys192Trp and c.501+4A>T.
- Treatment: Oral thiamine supplementation (600 mg/day) to increase substrate concentration for the residual TPK, magnesium supplementation (10 mmol/day).

Since then, less than 20 patients with TPK deficiency were reported. These patients presented after an initial normal development with episodic ataxia, psychomotor regression, dystonia and spasticity in their first years of life. Symptoms were often triggered by febrile illness. Biochemical studies revealed elevated serum and CSF lactate, and increased urinary α-ketoglutarate excretion. MRI showed mostly lesions of the basal ganglia and dentate nuclei. Some patients with TPK deficiency have been treated with thiamine. These patients stabilized or even improved clinically and survived longer compared to patients without thiamine supplementation.

Conclusion

TPK deficiency is a rare, but potentially treatable disorder of the thiamine metabolism. Our case outlines the importance of considering the group of thiamine responsive disorders and conducting appropriate genetic tests when patients present with acute-onset encephalopathy, ataxia and other signs suggesting a mitochondrial disorder. High dose thiamine supplementation may ameliorate the course of TPK deficiency and should be initiated promptly after diagnosis or even upon suspicion.

Disclosure: The authors report no conflicts of interest.