The SLC25A19 gene encodes the 320-residue mitochondrial Thiamine pyrophosphate transporter (hMTPPT). TPP, the activated form of thiamine, is an essential cofactor of three thiamine-dependent mitochondrial enzymes (PHD, branched chain 2-oxo acid dehydrogenase and the oxoglutarate dehydrogenase complexes that catalyze essential reactions involving the oxidative energy metabolism. SLC25A19 gene mutations gene impair the function of the thiamine mitochondrial carrier, leading to two distinct clinical phenotypes: Amish lethal microcephaly, and the second phenotype is characterized by bilateral striatal necrosis and peripheral polyneuropathy. Early thiamine supplementation may improve the outcome.

A 5-month-old boy, product of consanguineous marriage. He was normal till the age of 2 months. Then he presented recurrent acute encephalopathy following febrile illness, and frequent seizures. On examination, he was failure to thrive, hypotonic, microcephalic (HC at 10 percentile), lack of contact and interaction, and absent deep tendon reflexes. Laboratory investigations showed persistent lactic acidosis (up to 7 mmol/l). MRI brain showed bilateral striatal necrosis and some brain volume loss (Figure 1). Electromyography showed a motor and sensory neuropathy. WES showed homozygous missense mutation in the SLC25A19 gene (c.904T>C; p.(Ser302Pro)). This mutation was validated by sanger sequencing, and the carrier status of the parents was confirmed. Patient started on thiamine supplementation (100 mg three times a day). He showed dramatical improvement in his alertness, tone, seizures frequency and duration, and lactic acidosis. During follow-up, he still has global developmental delay, but no further admissions for decompensation.
Diseases related to SLC25A19 mainly include Amish lethal microcephaly (MCPHA; OMIM #607196) and Thiamine metabolism dysfunction syndrome 4 (THMD4, OMIM #613710). THMD4 are characterized by episodes of encephalopathy in childhood that are often triggered by febrile illness. They usually suffer from encephalopathy, muscular weakness, and the disappearance of deep tendon reflexes. Patients’ brain MRI displays abnormal signals in bilateral basal ganglia, and some patients have high levels of lactic acid in CSF or sera.

In Biotin-Thiamine responsive basal ganglia disease, another inherited thiamine transporter defect, early supplementation with thiamine and biotin lead to significant improvement of the symptomatology. In SLC25A19-related diseases, supplementation of thiamine was associated with a variable response. This could be associated with the severity of the phenotype and the time of initiation of treatment. Treatment with thiamine supplementation at a dose of 400 mg/day can occasionally relieve symptoms.

**Discussion**

Early diagnosis of SLC25A19-related thiamine dysfunction syndrome is crucial as early and life long treatment with thiamine may have a significant impact on prognosis.

**Conclusion**

Early diagnosis of SLC25A19-related thiamine dysfunction syndrome is crucial as early and life long treatment with thiamine may have a significant impact on prognosis.

**References**