Infantile Leigh-like syndrome caused by SLC19A3 mutations is a treatable disease

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Sir,

The research articles ‘Exome sequencing reveals mutated SLC19A3 in patients with an early-infantile, lethal encephalopathy’ by Kevelam et al. (2013) and ‘Exome sequencing reveals a novel Moroccan founder mutation in SLC19A3 as a new cause of early-childhood fatal Leigh syndrome’ by Gerards et al. (2013) describe a novel disease entity of an infantile Leigh-like disorder caused by SLC19A3 mutations. In the study of Gerards et al. (2013) only two children out of 10 survived early childhood. These patients received different vitamins including thiamine and one child was treated with additional biotin during later clinical course. However, important information such as dosages and exact time point of the start of treatment has not been provided. Moreover, outcome in these patients was unfavourable. In the study of Kevelam et al. (2013) all patients died during the first years of life. No thiamine was given to these children.

SLC19A3 encodes a thiamine transporter (hTHTR2), which is essential for cerebral thiamine metabolism (Zeng et al., 2005). Impaired hTHTR2 activity due to SLC19A3 mutations is known to cause biotin-responsive basal ganglia disease (BBGD; OMIM 607483), which is a childhood-onset disorder characterized by episodes with encephalopathy and subsequent neurological deterioration (Zeng et al., 2005; Tabarki et al., 2013). Untreated, this disease may be fatal but supplementation of biotin and thiamine (both 10–15 mg/kg/day) is highly effective and prevents further disease progression (Distelmaier et al., 2013). Based on this knowledge, one might expect that in the abovementioned early childhood condition a treatment with high-dose biotin and thiamine is effective. This idea is further strengthened by the observation of Gerards et al. (2013) that the only two patients with a longer survival received at least thiamine. In addition, Pérez-Dueñas et al. (2013) described an infant with a SLC19A3 missense mutation and early onset Leigh-like syndrome that responded well to a combined therapy with biotin and thiamine.

Here, we report on two affected boys born as the first (Patient 74115) and third (Patient 75709) child to healthy consanguineous Turkish parents. The second child of the family was unaffected. Patient 74115 suffered from neonatal-onset Leigh syndrome and died at the age of 2 months. Diagnosis was based on MRI findings with symmetrical basal ganglia and brainstem lesions and lactate peak on magnetic resonance spectroscopy (Fig. 1A–D), as well as elevated lactate in blood. Biochemical diagnostics in fresh muscle tissue revealed a globally reduced mitochondrial ATP production rate. However, there was no disturbance of a specific respiratory chain complex. Biochemical investigation of cultured fibroblasts was normal. At that time, no genetic cause was identified and no thiamine or biotin treatment was initiated.

The younger brother, Patient 75709, had a normal pregnancy and perinatal period. However, at the age of 18 days he was...
admitted because of irritability, seizures and vomiting. Laboratory testing revealed increased blood lactate of maximal 7.0 mmol/l (normal range <1.6 mmol/l) and CSF lactate of 4.0 mmol/l (normal range <2.8 mmol/l). Brain MRI showed an almost identical lesion pattern as the brother (Fig. 1E–H). Based on the recently published cases of SLC19A3 mutations associated with infantile Leigh syndrome, an empirical treatment with biotin (10 mg/kg/day) and additional thiamine (15 mg/kg/day) was started immediately (Distelmaier et al., 2013). This medication clearly improved his clinical status within ~2 weeks. Blood lactate dropped to normal levels and seizures, as well as irritability, subsided completely. During medical follow-up, the boy showed adequate developmental progress. Brain MRI at the age of 4 months revealed a substantial regression of lesions in basal ganglia, brainstem, and subcortical regions (Fig. 1I–L). Of note, some degree of frontotemporal brain atrophy was detected, which might resemble residual damage after the initial metabolic crisis.

Figure 1  Brain MRI findings in Leigh-like syndrome caused by SLC19A3 mutations. T2-weighted brain MRI sequences of Patient 74115 (A–C) demonstrating bilateral hyperintensity in cortical areas (A), basal ganglia (B), and brainstem (C). Abnormalities are indicated by white arrows. Single voxel spectroscopy (D) showing an intense lactate peak at 1.35 ppm (white arrow) and a reduced N-acetyl-aspartate peak. T2-weighted sequences and single voxel spectroscopy of Patient 75709 (E–H), revealing an almost identical lesion pattern compared to the brother. Abnormalities are indicated by white arrows. T2-weighted sequences and single voxel spectroscopy of Patient 75709 (I–L) 3 months after start of treatment with biotin and thiamine, showing complete resolution of basal ganglia, brainstem, and cortical alterations and disappearance of lactate peak in the single voxel spectroscopy. Of note, some degree of frontotemporal brain atrophy was detected, which might resemble residual damage after the initial metabolic crisis.
Patient 74115 (for methods details and sequencing statistics see the online Supplementary material). In line with a clinically suspected diagnosis of perturbed thiamine metabolism, exome sequencing revealed a novel homozygous frameshift mutation in \textit{SLC19A3}, c.[982del];[982del], p.[Ala328Leufs*10];[Ala328Leufs*10]. The mutation was absent from 7200 in-house control chromosomes and public databases. The 1 bp deletion is located in the fourth coding exon and predicts a truncated protein missing the last 160 amino acids (32% of the full length protein). Confirmatory Sanger sequencing showed the mutation in the homozygous state in the two affected brothers whereas the healthy parents were heterozygous carriers.

To date, including our study, five index cases carrying two clear \textit{SLC19A3} loss-of-function alleles have been reported (Gerards \textit{et al.}, 2013; Kevelam \textit{et al.}, 2013). All presented with early-onset, rapidly fatal Leigh-like syndrome. However, our observation suggests that a combined biotin/thiamine treatment is effective, even in the complete absence of hTHTR2. To date, a compensatory increase in the expression levels of mutant hTHTR2 with remaining residual activity was hypothesized as an explanation for the beneficial effects of biotin treatment in classical cases with BBGD. However, this mechanism is not applicable in hTHTR2 null patients. Gerards \textit{et al.} (2013) proposed a biotin-induced partially compensating upregulation of \textit{SLC19A2}-encoded hTHTR1 as an alternative mechanism. However, this idea is challenged by expression studies in brain vessels, suggesting that hTHTR1 is mainly present at the basement membrane while hTHTR2 is highly expressed at the luminal side (Kevelam \textit{et al.}, 2013). Therefore, an alternative thiamine uptake mechanism can be assumed. This idea is supported by the observation of Pérez-Duèñas \textit{et al.} (2013), who reported a clinical stable course of a Leigh-like infant with a \textit{SLC19A3} missense mutation, mainly treated with high-dose thiamine (20 mg/kg/day).

In conclusion, we would like to highlight that the infantile-onset, Leigh-like clinical presentation associated with loss-of-function mutations in \textit{SLC19A3} is a treatable disease. Immediate start of high-dose biotin and, in our view more importantly, thiamine treatment may be live-saving in these children and might be essential for neurodevelopmental outcome. Accordingly, also in unclear cases of early childhood Leigh syndrome, an empirical medication with biotin and thiamine is recommended.

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**Supplementary material**

Supplementary material is available at \textit{Brain} online.

**References**


