LETTER TO THE EDITOR

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

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Sir,

The letter by Haack et al. (2014) provides important information confirming the role of the thiamine transporter hTHTR2 in Leigh syndrome and the beneficial effect of biotin and/or thiamine treatment for patients harbouring mutations in the gene encoding hTHTR2, SLC19A3. In recent years many new pathogenic mutations have been reported in SLC19A3 resulting in several age-related neurological phenotypes like biotin-responsive basal ganglia disease (BBGD), Wernicke-like encephalopathy and Leigh syndrome and various responses to biotin and/or thiamine (Zeng et al., 2005; Kono et al., 2009; Debs et al., 2010; Yamada et al., 2010). The exact mechanism by which biotin and/or thiamine treatment results in alleviation of the phenotype or prevents further disease progression is still unclear, but the current data challenge the initial hypothesis that biotin-induced upregulation is the central mechanism. Table 1 summarizes all pathogenic mutations identified in SLC19A3 to date, the phenotypes caused by the mutations and whether biotin and/or thiamine treatment was successful. Based on the data available, no definite conclusion can be drawn, whether biotin, thiamine or both are crucial for further disease progression. Patients with the same mutation have been reported to respond to supplementation of biotin or thiamine alone (Zeng et al., 2005; Perez-Duenas et al., 2013). Furthermore, Alfadhel et al. (2013) reported on a study with 18 patients with BBGD in which one-third of the patients showed recurrence of acute crisis when treated with biotin alone, although carrying the same pathogenic mutation as the responsive individuals (Alfadhel et al., 2013). However, treatment of these patients with both biotin and thiamine resulted in complete absence of acute crisis. Therefore, they propose to rename BBGD to BTBGD (biotin-thiamine-responsive basal ganglia disease) as the addition of thiamine is clearly essential. It is highly suggestive, as illustrated in these studies and put forward by Haack et al. (2014) that the combination of biotin and thiamine is most effective.

A universal role for biotin treatment in SLC19A3 mutations was challenged in our paper, because the proposed biotin-induced upregulation of hTHTR2 could not explain the beneficial effect of biotin treatment in our patients with nonsense mutations (Gerards et al., 2013). A key role for thiamine was more likely and we proposed that the high amounts of thiamine administered would trigger an alternative transporter. We suggested the SLC19A2-encoded hTHTR1 as a possible candidate. Therefore, we did not propose an effect of biotin on SLC19A2 expression, as suggested by Haack et al. (2014), but on SLC19A3 expression. We agree with Haack et al. on the presence of an alternative transporter, but are not convinced that this could not be the SLC19A2-encoded hTHTR1. It has been proposed that high doses of thiamine might induce a biochemical change in hTHTR1, increasing the capacity for thiamine transport (Debs et al., 2010). In that way hTHTR1 could compensate for the hTHTR2 defect. Further functional studies should elucidate this issue.

Although treatment with biotin and/or thiamine alleviates the phenotype and prevents further disease progression in patients with SLC19A3 mutations, it is too early to conclude that these are fully treatable disorders. The patient reported by Haack et al. (2014) is still an infant and the beneficial effect of the thiamine treatment in the long-term has yet to be shown. Moreover, our patients received thiamine (100 mg/kg/day), and in one case also biotin (5 mg/kg/day), in infancy, but nevertheless died from the consequence of the SLC19A3 mutations in the second decade of life. More studies are warranted to illustrate the long-term effect of treatment with biotin and/or thiamine in case of SLC19A3 mutations, the mechanism in which they work and
whether additional environmental or genetic factors play a role in the efficiency of biotin and/or thiamine treatment. Nevertheless, current data clearly illustrate the benefits of biotin and/or thiamine in patients with SLC19A3 mutations, at least in the short term. Therefore, patients with suspected thiamine transport deficiency should be pre-emptively treated with both biotin and thiamine. It makes sense, as Haack et al. stress, to also do this in uncertain cases, where a genetic diagnosis still has to be established.

**Funding**

The work is supported by the Alma in Silico project, which is financed by the Interreg IV European funds, The Walloon Region, The North Rhine Westphalia, The Flemish Community, The Belgian Province of Limburg and The Dutch Province of Limburg, as well as by the Universities of Maastricht and Liège, by the Princes Beatrix Spierfonds (grant W.OR11-24) and the Stichting Metakids.

**References**


