Chapter 3.2

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

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Sir,
We are grateful for the opportunity to respond to the correspondence from Haack et al. and thank the authors for their interest in our recent paper on seven patients with early-infantile, lethal encephalopathy caused by SLC19A3 mutations. In their letter, the authors present two brothers with an early onset Leigh-like clinical presentation. The first boy died at the age of 2 months. The second was treated with thiamine and biotin from the day he presented (18 days old), with striking clinical improvement. Before treatment MRI showed bilateral signal abnormalities in limited areas of the cerebral cortex and in the basal nuclei, thalami and brainstem (Figure 1, A). With treatment, the signal abnormalities disappeared, although significant cerebral atrophy was seen on the MRI at the age of 4 months (Figure 1, C). The atrophy as shown in Figure 1 is more severe than suggested by the text of the letter (compare Figure 1, C and D).

Figure 1. Cerebral MRI images illustrating the differences between the patient of Haack et al. (2014), one of our patients and a healthy infant. Axial T2-weighted images, obtained at presentation, show localized abnormalities in Patient 75709 (arrows in A), whereas extensive involvement of virtually the whole brain is seen in our patient (B). Axial T2-weighted images of Patient 75709, obtained 3 months after starting treatment, show disappearance of the signal abnormalities but also significant brain atrophy (C) as compared to the age-matched control (D).

These findings are, of course, highly promising. Our study concerned the retrospective diagnosis in seven patients, who had all died before the study was performed. Because of the retrospective nature of our study, we were not able to assess the effects of early treatment in our cases. Considering the severe encephalopathy and the impressive MRI abnormalities showing near-complete grey matter degeneration in all areas of the brain at presentation (Figure 1, B), we were rather pessimistic about the possible beneficial effects of thiamine and biotin in such cases and considered that treatment soon after presentation may already be too late to prevent severe permanent brain damage. Two
of our patients had received biotin without clinical effects. But perhaps we should revise our concerns.

Although it is important to avoid therapeutic negativism and not give up on patients who have a treatable condition, it is equally important to avoid the devastating neurological handicap associated with treatment that has been started too late. We would like to stress that the clinical severity of the encephalopathy and MRI findings at presentation should be considered. Evidently, our patients were even more severely affected than the brothers described in the present letter.\textsuperscript{1,2} They had more extensive MRI abnormalities with virtually diffuse cerebral cortical involvement and also more extensive grey matter abnormalities elsewhere (compare Figure 1, A and B). We do not know what the outcome would be if thiamine and biotin treatment was started in such patients. But we also do not know what the outcome of the present patient will be.\textsuperscript{1} Considering the fact that the follow-up was only up to the age of 4 months and MRI at 4 months shows significant cerebral atrophy (Figure 1, C), we are concerned about the long-term outcome. We would like to invite Haack et al. to describe the outcome of their patient again after 6 and 18 years.

The present title of the paper, ‘Infantile Leigh-like syndrome caused by SLC19A3 mutations is a treatable disease’ suggests complete or almost complete recovery upon treatment, which must still be proven. As such, we would have preferred a more cautious title of the letter.

REFERENCES
