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Respiratory failure in *NDUFS1*-related Leigh syndrome with normal cerebral MRI suggests alternative etiologies

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Abstract
Leigh syndrome is clinically characterised by a multisystem phenotype in which encephalopathy is the most striking feature. Cerebral MRI shows symmetric T2-hyperintense lesions in the basal ganglia, thalamus, midbrain, brainstem, and cerebellum. The genetic background is heterogeneous with mutations in >75 different genes. Leigh syndrome due to variants in NDUFS1 has been repeatedly reported and is biochemically characterised by complex-I deficiency. Description of new cases is warranted. If the course is fatal, autopsy should be carried out. To broaden the knowledge about Leigh syndrome and carriers of NDUFS1 variants, these patients require comprehensive work-up.

Keywords: Mitochondrial Disorder, Leigh Syndrome, NDUFS1, Compound Heterozygous, Complex-I Deficiency, Respiratory Chain

Letter to the Editor

We read with interest the article by Men *et al*. about a new-born with Leigh syndrome due to the heterozygous variants c.64C>T and c.584T>C in *NDUFS1* [1]. Two days after birth the patient was admitted for poor feeding and respiratory insufficiency requiring intubation and mechanical ventilation [1]. Despite maximal treatment, the patient succumbed on hospital day 30 [1]. The study is appealing but has several limitations that raise concerns that should be discussed.

Missing is the determination of lactate in the cerebro-spinal fluid (CSF) [1]. Missing is also a magnetic resonance spectroscopy (MRS), which frequently shows a lactate peak in abnormal or normally appearing cerebral regions [2]. Lactic acidosis in the brain could explain respiratory failure even in the absence of structural cerebral lesions.

Missing is an explanation why the initial cerebral MRI on hospital day 8 was normal, whereas the cerebral MRI on hospital day 30 revealed bilaterally symmetric lesions of the basal ganglia, cerebral peduncles, and the brainstem, which were hypointense on T1, and hyperintense on T2 and diffusion-weighed imaging (DWI) [1]. It should be discussed if respiratory insufficiency on admission was not due to a brainstem lesion but rather due to lactic acidosis or due to weakness of respiratory muscles. It should be reported if there were any indications for myopathy, such as ptosis, ophthalmoparesis, limb weakness, elevation of creatine-kinase (CK). We should be informed if a muscle biopsy had been carried out to prove or disprove the presence of myopathy. An indication for myopathy in the index patient could be hypotonia reported on hospital day 10. Was a needle electromyography carried out and was it myogenic?

Missing is the information if there was pulmonary hypertension, pulmonary embolism, or right ventricular dysfunction, which all could explain cyanosis. Pulmonary hypertension has been previously reported as a manifestation of respiratory chain complex-I deficiency [3]. Pulmonary embolism may result from exsiccosis due to poor feeding or reduced mobility due to muscle weakness. Atelectases found on chest radiography on hospital day 2 could be due to pulmonary embolism. Right ventricular dysfunction could be due to a left to right shunt on the atrial level from the patient foramen ovale. We should know if there was congestion of the liver or hepatosplenomegaly. Was the pro-brain natriuretic peptide (pro-BNP) elevated in the index patient?

Missing is the information of the causative *NDUSF1* variants occurred in cis or trans. Do these variants have to be regarded as compound heterozygous?

We disagree with the notion that cyanosis was the initial phenotypic manifestation of Leigh syndrome. The initial manifestation was most likely poor feeding and crying. We also disagree with the notion that electroencephalography is capable to show delayed development [1].

Missing are the autopsy findings of the patient.
Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Fatal Leigh syndrome requires comprehensive work-up, including autopsy.

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