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Letter to the Editor

Leigh/MELAS overlap syndrome due to the variant m.10191T>C

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With interest we read the article by Ko and colleagues about a 4yo male with a mitochondrial disorder (MID) due to the variant m.10191T>C in *ND3*, which was classified as Leigh/MELAS overlap syndrome (Ko, A., & Lee, Y. M. 2019). We have the following comments and concerns.

We disagree with the classification of the condition as Leigh/MELAS overlap syndrome (Ko, A., & Lee, Y. M. 2019). Phenotypic hallmarks of MELAS are stroke-like episodes (SLEs) showing up on multimodal MRI as stroke-like lesions (SLLs), basal ganglia calcification, diffuse leukoencephalopathy, headache, epilepsy, confusion, psychiatric abnormalities, or vomiting (El-Hattab, A.W. *et al.*, 2001). Since none of these classical phenotypic features of MELAS was present in the index patient (Ko, A., & Lee, Y. M. 2019), it is not justified to characterise the condition as MELAS. The presence of a lactate peak on MRS is non-specific since it occurs also in a number of other MIDs (table 1). Lactate peaks have been particularly reported in CPEO, LS, MERRF, LTSL, LBSL, SANDO, MIMODS, DDS, and ME (table 1).

Table 1. MIDs in which MRS revealed lactate peaks

Syndrome	Mutation	Reference
MERRF	m.8344A>G	(Catterrugia *et al.*,. 2015)
LS	m.9176T>C	(Chourasia *et al.*,. 2017)
MELAS	m.3243A>G	(Lee *et al.*,. 2018)
LTBL	*EARS2*	(Oliveira *et al.*,. 2017)
LBSL	*DARS2*	(Kassem *et al.*,. 2014)
SANDO	*POLG1*	(Tanaka *et al.*,. 2013)
CPEO	np	(Chi *et al.*,. 2011)
Pearson syndrome	np	(Chi *et al.*,. 2011)
DDS	np	(Chi *et al.*,. 2011)
ME	np	(Lee *et al.*,. 2010)
MIMODS	np	(Karkare *et al.*,. 2008)
MCAS	no	(Boddaert *et al.*,. 2008)
MIMODS	mtDNAdel	(Vedolin *et al.*,. 2006)
AHS	np	(Ulmer *et al.*,. 2002)

MERRF: myoclonic epilepsy with ragged-red fibers, LS: Leigh syndrome, LTBL: leukoencephalopathy involving the thalamus and brainstem with high lactate, LBSL: leukoencephalopathy with brainstem and spinal cord involvement, SANDO: DDS: deafness dystonia syndrome, ME: mitochondrial encephalopathy, MIMODS: mitochondrial Multiorgan disorder syndrome, MCAS: mitochondrial cerebellar ataxia

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syndrome, AHS: Alpers Huttenlocher disease, np: not provided

Missing in this report is the mutation load (Ko, A., & Lee, Y. M. 2019). For interpretation of the pathogenicity of the variant in the presented patient it is crucial to know the heteroplasmy rate of the variant m.10191T>C not only in muscle but also in hair follicles, buccal mucosa cells, skin fibroblasts, lymphocytes, and urinary epithelial cells. Heteroplasmy rates frequently correlate with the severity of the phenotype.

Missing is also a thoroughly taken family history (Ko, A., & Lee, Y. M. 2019). Since mtDNA variants are transmitted via a maternal trait of inheritance in up to 75% of the cases (Poulton, J. *et al.*, 2017), we should be informed if the mother or any other first degree relative carried the *ND3* variant as well or manifested clinically with features reported in the patient or other typical MID features.

A further shortcoming of the report is that the pathogenicity of the m.10191T>C variant was not confirmed by application of the modified Yarham score (Finsterer, J. *et al.*, 2018).

Progression of Leigh syndrome during the disease course is typical for most of the patients and it is thus not surprising that cerebral involvement increased over time. Lactate elevation in brain thus may be absent at onset but may become apparent during the further disease trajectory.

Overall, this interesting case could be more meaningful if heteroplasmy rates in various tissues and an extensive family history were provided, if the syndrome was reclassified as Leigh syndrome, and if the pathogenicity of the variant was confirmed by application of the modified Yarham score (Finsterer, J. *et al.*, 2018).

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