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Letter To The Editor

Does NDUFS3-Mediated Cell Death Contribute To the Phenotype of NDUFS3 Mutations C.418C>T and C.595C>T?

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With interest we read the article by Lou *et al.*, (2018) about a male in whom Leigh syndrome (LS) was diagnosed at age 7 months and who died at age 2 years. He manifested clinically with lactic acidosis, torticollis, leucoencephalopathy, and T2-hyperintensities in the basal ganglia and brainstem (Lou, X., *et al.*, 2018). The genetic cause of LS was the complex heterozygous mutations c.418C>T and c.595C>T in the *NDUFS3* gene (Lou, X., *et al.*, 2018). Follow-up MRI at age 1 year showed progression of the cerebral lesions (Lou, X., *et al.*, 2018). We have the following comments and concerns.

The description of the phenotype is thrifty. It would be helpful for establishing genotype phenotype correlations to exactly know which phenotypic manifestations were present at diagnosis and which developed over the course. Patients with LS not only manifest in the brain but also in other organs, such as the eyes, ears, endocrine organs, heart, or gastrointestinal tract (Sofou, K. *et al.*, 2018). In the muscle patients with LS may manifest as ophthalmoplegia, myopathy of the limb muscles, or scoliosis (Sofou, K. *et al.*, 2018; Benit, P. *et al.*, 2004). In the eyes optic atrophy may be found (Benit, P. *et al.*, 2004). Otologic manifestations include hypoacusis. In the brain LS may additionally manifest with ataxia, spasticity, failure to thrive, generalised hypotonia, nystagmus, dysphagia, central hypoventilation, dyskinesia, axial dystonia, or epilepsy (Sofou, K. *et al.*, 2018; Benit, P. *et al.*, 2004). In the heart LS manifests with cardiomyopathy or arrhythmias (Ogawa, E. *et al.*, 2017). Gastrointestinal manifestations include hepatopathy with liver failure, pancreatitis, or intestinal pseudo-obstruction (Benit, P. *et al.*, 2004; Itai, T. *et al.*, 2018). Which of these manifestations were found in the index case?

The index patient carried two mutations in the *NDUFS3* gene and both were regarded as pathogenic (Lou, X., *et al.*, 2018). Since the father carried the mutation c.418C>T and the mother the mutation c.595C>T, it is conceivable that both of them manifested clinically. Which were the clinical manifestations in the parents of the index case? Did the mother also manifest with LS since the mutation c.595C>T has been previously reported in association with LS (Benit, P. *et al.*, 2004). Was severity of clinical manifestation similar or dissimilar in both parents and between the index case and parents? Were also other first-degree relatives investigated?

Cleavage of NDUFS3 by granzyme-A represents a novel pathway of programmed cell death (Lieberman, J. 2010). Cleavage of NDUFS3 disrupts the mitochondrial metabolism and generates reactive oxygen species (ROS) which drive the endoplasmatic reticulum-associated SET complex into the nucleus, where it activates single-stranded DNA damage (Lieberman, J. 2010). Cells that are resistant to the caspases or GzmB by overexpressing bcl-2 family anti-apoptotic proteins or caspase or GzmB protease inhibitors, are sensitive to GzmA (Lieberman, J. 2010). Did affection of this pathway contribute to the pathogenicity of the two mutations?

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To summarise, this interesting case could be more meaningful if the phenotype of the index case and of his parents would have been described in detail and if the influence of the mutations on the function of NDUFS3 in the novel pathway of programmed cell death would have been discussed.

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