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Letter to the Editor

Beneficiality of Mtor Inhibitor Everolimus for Mitochondriopathy Requires Evidence Based Proof

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In a recent article, Sage-Schwaede *et al.*, reported about a 2yo female with Leigh syndrome due to the homozygous variant c.355G>C in *NDUFS4*, and a 4yo male with MELAS due to the variant m.3243A>G in *MT-TL1*, who both were treated with the mTOR inhibitor everolimus (2-4mg/d), a rapamycin analogous (Sage-Schwaede, A. *et al.*, 2019). During the treatment period of 24 months the patient with Leigh syndrome improved phenotypically, while the patient with MELAS died after a treatment period of 10 months (Sage-Schwaede, A. *et al.*, 2019). The study has a number of shortcomings.

The main shortcoming of the study is the design. To assess the therapeutic effect of a drug, a sufficiently large number of patients needs to be treated in a multi-center, double-blind, placebo-controlled, cross-over design. Since such a design was not applied, the conclusions are not justified. Improvement in the patient with Leigh syndrome may reflect the natural disease course or could be due to treatment with compounds other than everolimus, such as coenzyme-Q or thiamin.

The second shortcoming is that the current medication other than everolimus was not reported. Knowing the medication a patient is regularly taking is crucial with regard to assessing the beneficial effect of the study drug, possible interactions, and with regard to adverse reactions. From coenzyme-Q and thiamine, for example, it is well-known that it may exhibit a beneficial effect in some types of Leigh syndrome (Van Maldergem, L. *et al.*, 2002). From some antiepileptic drugs it is known that they can be mitochondrion-toxic (Finsterer, J. 2017). From steroids, statins and fibrates it is known that they may worsen mitochondrial myopathy (Chariot, P. *et al.*, 1993). From local anesthetics it is known that they can deteriorate muscle weakness in mitochondrial disorder (MID) patients.

A third shortcoming is that mTOR inhibitors per se can induce myopathy (Finsterer, J. *et al.*, 2003). Thus, it is conceivable that deterioration on the MELAS patient was due to a toxic effect everolimus. Whether such an adverse reaction occurs only in patients with subclinical or mildly manifesting pre-existing myopathy is unknown. Anyhow, it should be discussed if continuous decline in the MELAS patient was attributable to involvement of the central nervous system (CNS) or to involvement of the muscles, or to the toxic effect of everolimus. We should also be informed about the cause of death, particularly if there was weakness of the respiratory muscles resulting in muscular respiratory failure, if there cardiac involvement, or if there was intractable seizure activity.

We do not agree with the statement that the high heteroplasmy rate of the m.3243A>G variant in the index patient (78%) compared to the heteroplasmy rates in lymphocytes of the four MELAS patients with a kidney transplant (5-20%) has no effect on the phenotypic variability and the variable reaction to everolimus. In some cases there is of course a correlation between lymphocytic heteroplasmy and phenotype, why we should know if heteroplasmy rates were determined in tissues other than lymphocytes to confirm the correlation and if there was a difference in

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the heteroplasmy rate between the index patient and his mother who also manifested clinically.

Overall, this interesting study could be more meaningful if the conclusions were supported by evidence-based results, if heteroplasmy rates were determined in tissues other than lymphocytes, if the current medication of the cases was provided, and if the toxic effect of everolimus was discussed with regard to the continuous deterioration of the MELAS patient respectively his death.

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