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Letter to the Editor

Unaddressed Issues in Carriers of COQ2 Variants

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In a recent article, Eroglu *et al.*, reported about 4 pediatric patients with primary coenzyme-Q deficiency due to the homozygous mutation c.437G>A in the *COQ2* gene (Eroglu, F. K. *et al.*, 2018). Phenotypically, the four patients presented with microcephaly, ischemic stroke, stroke-like episodes, epilepsy with intractable seizure activity, optic atrophy, respiratory insufficiency, vomiting, lactic acidosis, hyperglycemia, and renal insufficiency with proteinurea and hyponatriemia (Eroglu, F. K. *et al.*, 2018). We have the following comments and concerns.

A shortcoming of the case study is that it is not mentioned if patient 1 and patient 2 originated from consanguineous parents, and if either parent also carried the *COQ2* variant in a heterozygous form. The same is true for patient 3 and patient 4. Since all four patients carried the same variant, we should be informed if the two families were truly unrelated or if they originated from the same village or region.

Cerebral MRI of patient 1 unambiguously shows cortical cytotoxic edema bilaterally, suggesting embolic stroke (Eroglu, F. K. *et al.*, 2018). Thus, we should be informed if the patient carried cardiovascular risk factors in addition to diabetes, such as atrial fibrillation, systolic dysfunction, arterial hypertension, or hyperlipidemia. A cytotoxic edema may be occasionally also found in patients with stroke-like episodes (SLEs) (Tzoulis, C., & Bindoff, L.A. 2009), which manifest on MRI as stroke-like lesions (SLLs), or in patients with seizures. Thus, we should be informed about the outcome of these lesions. SLLs may progress, regress, disappear, or may change into cortical laminar necrosis, toe-nail sign, cysts, or white matter lesions (Finsterer, J., & Zarrouk-Mahjoub, S. 2018). It should be also mentioned if the MRI was carried out peri-ictally and if the EEG at the time of the MRI showed epileptic activity.

Patient 4 is described as having had developed SLLs, the morphological equivalent of a SLE (Eroglu, F. K. *et al.*, 2018). Treatment of SLEs usually includes application of NO-precursors, non-mitochondrion-toxic antiepileptic drugs (AEDs), and steroids (Fryer, R.H. *et al.*, 2016). We should be informed how the SLE manifested clinically in patient 4 and which type of therapy for the SLE was administered. There are also single case reports showing a beneficial effect of midazolam, the ketogenic diet, or CoQ for SLLs.

Patient 1 and 2 developed intractable seizures. However, it is not mentioned which AEDs were applied and which dosage was maximally chosen. From certain AEDs it is well known that they can be mitochondrion toxic (Finsterer, J., & Zarrouk Mahjoub, S. 2012). Particularly from valproic acid, carbamazepine, phenytoin, and phenobarbital it is known that they may be mitochondrion-toxic and thus trigger, prolong, or aggravate seizure activity. Thus, we should be informed which AEDs in which dosage and combination were given over which time. Since refractory epilepsy in mitochondrial disorders may respond to the ketogenic diet, we should be informed if this type of nutrition was tried and if it exhibited a beneficial effect.

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Overall, this interesting case study could be more meaningful if more information about the AED therapy would have been provided, if the ketogenic diet would have been applied, if parents were genetically tested for the causative mutation, if treatment of SLEs would have been discussed, and if treatment of SLEs would have been reported.

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