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Phenotypic spectrum of maternally inherited Leigh Syndrome associated with the m.8993T > G variant

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Dear Editor,

We appreciate the Letter to the Editor by Drs. Finsterer and Zarrouk-Mahjoub [1] in response to our publication in *Molecular Genetics and Metabolism* "Novel insights into the functional metabolic impact of an apparent *de novo* m.8993T > G variant in the *MT-ATP6* gene associated with maternally inherited form of Leigh Syndrome" [2]. The authors inaccurately concluded that normal development of the proband was interrupted by vaccinations [1]. We did not provide corroborative evidence from fetal/perinatal MRI and ^{1}H-MRS assessing brain development and metabolic profile [2–4]. This variant causes clinical manifestations of Leigh Syndrome (LS) due to defects of mitochondrial oxidative phosphorylation and its near homoplasmic levels concord with the timing of LS onset [5]. The patient experienced regression coinciding with vaccination, a decision made by his home team preceding his referral to us [2]. A full sepsis workup, including a lumbar puncture, ruled out meningoencephalitis, prompting a metabolic workup and thus the diagnosis of LS.

A hypoxic event with pneumonia may explain ventriculomegaly in the second MRI, which is commensurate to the degree of cortical and white matter volume loss, commonly part of the sequence of the disease [5]. It does not indicate obstructive hydrocephalus, but rather hydrocephalus *ex vacuo*, a diagnostic concordant with absence of elevated intracranial pressure on examination for which a ventriculo-peritoneal shunt is not recommended.

The patient showed a good response to prednisone for infantile spasms. For insurance reasons, ACTH and vigabatrin were not chosen as first-lines of treatment. Ketogenic diet, which was declined by the parents, may not be effective for infantile spasms [6].

While this variant may cause neuropathy, retinitis pigmentosa, myopathy and renal dysfunction, the patient exhibited none of these phenotypic features. Thus, the phenotypic spectrum observed among LS patients may result from the patient's nuclear genome background and heteroplasmy of the m.8993T > G variant.

Conflict of interest

There are no conflict of interest to disclose.

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