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Response to letter to the editor: Why does Leigh syndrome responds to immunotherapy?

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We appreciate Dr. Finsterer et al. [1] interest in our case report [2]. They express doubts about the diagnosis of Leigh syndrome (LS). Our patient's diagnosis was based on the presence of a known ATPase 6 gene pathogenic mutation (T9176C), previously described in other LS cases [3–8] , and also in a form of hereditary spastic paraplegia [9] leukodystrophy [10] and bilateral striatal necrosis [11].This mutation has been shown to affect ATP synthesis and the assembly or stability of complex V [9,12]. There was no consanguinity in her family. The mother and other relatives refused genetic testing for personal (life insurance) and financial reasons. Patient and family also refused to have muscle biopsy done as she clinically improved. Magnetic resonance spectroscopy (MRS) was not performed because genetic testing found a known pathogenic mtDNA mutation. Regarding follow up imaging, brain MRI done 1 year later showed improvement in bilateral basal ganglia and periaqueductal region T2 hyperintensities. Patient did have a staring spell, with decreased oxygen saturation and was started on levetiracetam after her second admission. There was no family history of epilepsy. We agree with Dr. Finsterer et al. comprehensive list of POLG mutation-associated diseases. Regarding treatment effect, we want to reiterate that the exact mechanism by which plasmapheresis or immunoglobulin (IVIG) had beneficial effect in our patient is unknown; however as mentioned in the article, we think that reduced ATP production can increase the mitochondrial transmembrane potential (with resultant hyperpolarization) and increase reactive oxygen species (ROS) production [13], which can in turn activate the necroptosis pathway [14]. Impaired ATP synthesis can also induce necroptosis [15]. Resultant cell necrosis can lead to release of immunogenic material and activate immune and inflammation pathways (inflammasome) [14,16]. IVIG has been shown to suppress inflammasome-mediated neuronal death in ischemic stroke models [17]. Of note, in mice, mitochondrial complex I mutations have been shown to cause inflammation and retinal ganglion cell death [18], further highlighting the possible relationship between mitochondrial mutations/diseases and inflammation. Additionally, a case of mitochondrial myopathy responsive to intravenous immunoglobulin [19] and patients with acute central nervous system inflammation possibly associated with ND4 and DARS2 mutations and responsive to plasmapheresis, steroids and rituximab have been described in a small report [20]. Further research in the role of autoimmunity and inflammation in mitochondrial disease is needed.

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