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Correspondence

Reply to Cerebral Infarction in *CARS2* Mutation

To the Editor:

We appreciate the opportunity to respond to Dr. Finsterer's letter.[1] We want to discuss three issues: alternative treatment (other than conventional antiepileptic medicines) used in the treatment of super-refractory status epilepticus in this patient, her cardiac evaluation, and the possible pathogenesis of stroke in this patient with compound heterozygous pathogenic variants of the *CARS2* gene.

First, as described in the original article, the child was treated with both corticosteroid (methylprednisolone) and intravenous arginine infusion with no change in her seizures.[2] She also tried a ketogenic diet (4:1 ratio of fat: carbohydrate plus protein). However, she did not benefit from the diet nor was there a definite improvement in her cognitive status. The diet was withdrawn after six weeks as she developed acute pancreatitis.

Her cardiac evaluation was unremarkable with no evidence of cardiomyopathy, pre-excitation, or arrhythmia during her prolonged stay in the intensive care.

Her brain pathology is consistent with cellular injury and infarction. However, the exact pathogenesis of her stroke is undetermined as with most cases of mitochondrial dysfunction. Her left hemispheric lesion showed hypointensity on the apparent diffusion coefficient map and suggests a predominant cytotoxic process during the neuroimaging. However, a vasogenic process due to a persistent and severe hyperperfusion from blood-brain barrier dysfunction might have existed preceding the cytotoxic injury. Vasogenic edema with hyperperfusion has been reported previously in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome.[3] A subset of patients may have a combination of vasogenic and cytotoxic edema in neuroimaging. Our patient's left hemispheric lesion was not consistent with a cardioembolic or atherothrombotic stroke. The actual inciting factor of stroke in mitochondrial diseases is often unknown; however, microangiopathy due to mitochondrial dysfunction has been proposed as a possible etiology.[4] Alternatively, a defect in the oxidative phosphorylation process and energy failure might be responsible.[5] In our patient, a predominant involvement of the left hemisphere was seen in the acute phase. Progressive edema and then an atrophic process was seen but predominantly remained lateralized to the left hemisphere. The etiology of the progressive neuronal injury may be secondary to excitotoxicity from the continuing lateralized seizures or due to an exaggerated depolarizing phenomenon similar to the cortical spreading dispersion.

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