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Correspondence

Reply to Finsterer Regarding Lethal *NARS2*-Related Disorder Associated With Rapidly Progressive Intractable Epilepsy and Global Brain Atrophy

We appreciate the opportunity to respond to the comments of Dr. Finsterer. The details of antiepileptic treatment are provided. It is our opinion that seizure activity monitored by continuous electroencephalography remained constant and refractory to therapy. It did not appear to be worsened by medication choices or by various combinations and is more likely the result of the underlying genetic abnormality.

Patient 1

Initial treatment included intravenous (IV) lorazepam (0.1 mg/kg ×2), fosphenytoin (20 mg/kg), and levetiracetam (40 mg/kg). Initial phenobarbital (20 mg/kg plus 10 mg/kg IV) loads were not effective. Pentobarbital infusion was used for two weeks and then transitioned to scheduled phenobarbital. Lorazepam (0.15 mg/kg IV) boluses were employed periodically. Oxcarbazepine was added 18 days after presentation. He remained on multiple antiepileptic medications, namely, clobazam (1.25 mg/kg/day), levetiracetam (80 mg/kg/day), oxcarbazepine (40 mg/kg/day), phenobarbital (5 mg/kg/day), and topiramate (18 mg/kg/day), at the time support was withdrawn.

Patient 2

At presentation, lorazepam (0.1 mg/kg ×4) was used followed by fosphenytoin (20 mg/kg + 10 mg/kg). IV pentobarbital was used and transitioned to phenobarbital. Lacosamide (4 mg/kg/day) was added followed by levetiracetam (100 mg/kg/day) and vitamin B6 (pyridoxine) at 100 mg daily. Midazolam infusion was titrated up to 0.6 mg/kg/hour followed by IV ketamine (0.5 mg/kg then up to 2 mg/kg/hour). Ketogenic diet was started on day nine after admission. Midazolam infusion was transitioned to clobazam and clonazepam. Boluses of midazolam and levetiracetam were used periodically as needed. Phenobarbital was used successfully only for prolonged seizures. His discharge regimen included ketamine (104 mg/kg/day), lacosamide (6.8 mg/kg/day), levetiracetam (68 mg/kg/day), clobazam (2.7 mg/kg/day), phenobarbital (26.6 mg/kg/day), topiramate (6.8 mg/kg/day), and clonazepam for breakthrough clusters (0.25 mg every 4 hour). Complete seizure control was never achieved.

Regarding the characterization of magnetic resonance diffusion abnormalities, both patients demonstrated progressively widespread restricted diffusion as described in our report. We chose diffusion-weighted images to illustrate the unusual tiny symmetric restricted diffusion abnormalities in the mesencephalon because of the hypointensity of these lesions on the apparent diffusion coefficient maps, which could not have been reliably reproduced in publication.

Patient 2 underwent a screening echocardiogram two days after admission, which showed global depression of left ventricular function with left ventricular ejection fraction of 45%, with normal anatomy. No further study was performed.

Both boys had persistent thrombocytosis (477,000/μL to 831,000/μL). We recognize that hematologic abnormalities can be associated with mitochondrial disorders, although generalized marrow suppression and thrombocytopenia are more common. Patient 2 developed normocytic hypochromic anemia, apparently the most common subtype.[1]

Reference

1. Finsterer J, Marlies F. Hematologic abnormalities in mitochondrial disorders. Singapore Med J. 2015;56:412–419.

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