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Clinical Observations

Infantile Epileptic Encephalopathy Associated With *SCN2A* Mutation Responsive to Oral Mexiletine

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ABSTRACT

BACKGROUND: Genetic alterations are significant causes of epilepsy syndromes; especially early-onset epileptic encephalopathies and voltage-gated sodium channelopathies are among the best described. Mutations in the *SCN2A* subunit of voltage-gated sodium channels have been associated with benign familial neonatal-infantile seizures, generalized epilepsy febrile seizures plus, and an early-onset infantile epileptic encephalopathy. **METHOD:** We describe two infants with medically refractory seizures due to a *de novo SCN2A* mutation. **RESULTS:** The first child responded to intravenous lidocaine with significant reduction in seizure frequency and was successfully transitioned to enteral mexiletine. Mexiletine was subsequently used in a second infant with reduction in seizure frequency. **CONCLUSION:** Class 1b antiarrhythmic agents, lidocaine and mexiletine, may be useful in infants with medically refractory early infantile epileptic encephalopathy secondary to mutations in *SCN2A*.

Keywords: channelopathies, antiarrhythmic agents, lidocaine, epilepsy

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What this paper adds:

- Treatment of seizures in early onset infantile epileptic encephalopathy with lidocaine and mexiletine.

Introduction

Voltage-gated sodium channels contain alpha and beta subunits that span the cell membrane. When transmembrane potential increases, the channels open, resulting in cell depolarization and action potential propagation. There are four known alpha subunits in neurons (*SCN1A*, *SCN2A*, *SCN3A*, and *SCN8A*), and all have been associated with epilepsy ranging from febrile seizures to epileptic encephalopathy. *SCN1A* has been determined to be one of the more common gene mutations identified in genetic epilepsy. The less common *SCN2A* mutations have been associated with benign familial neonatal seizures, generalized epilepsy with febrile seizures plus, and a rare severe epileptic encephalopathy presenting in the newborn period. *SCN2A*-associated disorders are known to be autosomal dominant in inheritance, and mutations associated with severe disease are often found to be *de novo*.[1-3]

Although many antiepileptics target sodium channels, these drugs may not control or even reduce seizure frequency in infantile epileptic encephalopathies. Some cardiac antiarrhythmics also target sodium channels; in particular, lidocaine and mexiletine are US Food and Drug Administration–approved class 1b antiarrhythmics used to treat ventricular tachycardias. The need for parental administration of the former and the black-box warning for arrhythmias for the latter limit their use, but both have been used to treat refractory epilepsy.[4,5]

We describe two children with *SCN2A*-related early infantile epileptic encephalopathy, which was medically

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refractory. The first infant experienced significant reduction in seizure burden with lidocaine infusion and was then successfully transitioned to enteral mexiletine. We were then able to repeat this experience in the second child.

Patient Description

Case 1

This girl was born at 36 weeks' gestation by urgent Cesarean section for preterm labor complicated by fetal decelerations and oligohydramnios. At birth, she weighed 2010 g and was briefly intubated for meconium aspiration. At day two of life, she developed clonic seizures involving the left arm, occasionally the right, and bicycling motion of the legs. She was started on phenobarbital but continued to have up to eight to ten events per hour, so phenytoin and then oxcarbazepine were added. At three weeks of age, she was transferred to our facility where video electroencephalogram (EEG) revealed more than 100 electroclinical seizures per day. These partial-onset seizures originated independently in the right centrotemporal region and the left frontocentral region and manifested clinically as chewing and arrhythmic dystonic posturing. The background EEG showed highly asynchronous bursts of intermixed frequencies alternating with attenuated background, consistent with a burst suppression pattern. At other times the EEG demonstrated a pattern typical for migrating partial seizures of infancy. Magnetic resonance imaging of the brain suggested polymicrogyria most prominent in the right perisylvian region. Various combinations of levetiracetam, phenytoin, oxcarbazepine, lacosamide, and topiramate were tried. Topiramate produced the greatest degree of seizure reduction, but she continued to have multiple seizures per day. She received pyridoxine (100 mg every 15 minutes for total 500 mg), pyridoxyl-5-phosphate, folinic acid, and a trial of the ketogenic diet without improvement.

An infantile epilepsy panel (GeneDx, Gaithersburg, MD) identified an *SCN2A* deletion and insertion at c.4610_4614delTCATGinsGCATC, which

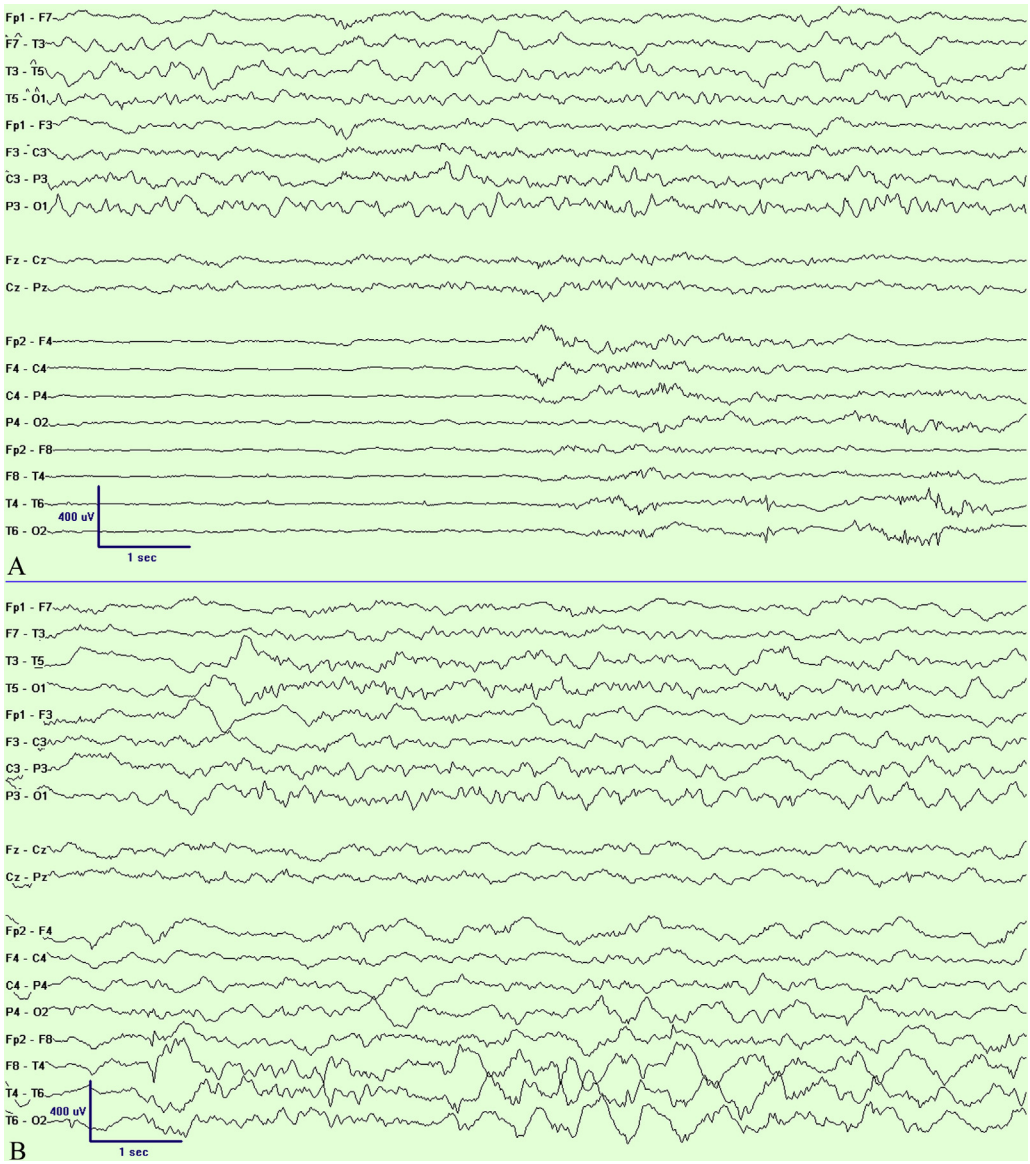

FIGURE.
Representative samples of electroencephalogram between epileptic seizures two hours prior to administration of lidocaine (A), showing right hemispheric burst-suppression pattern and left hemispheric slowing and four hours after administration of lidocaine (B), demonstrating improvement in the background with fast activity in the right temporal region and focal delta slowing. Bilateral independent seizures (not shown) decreased in frequency from hundreds per day to a couple per day. (The color version of this figure is available in the online edition.)