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Rapamycin Reduces Seizure Frequency in Tuberous Sclerosis Complex

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Abstract

The authors present a 10-year-old girl with tuberous sclerosis complex who has been receiving rapamycin for 10 months for seizure control. She was started at 0.05 mg/kg/d and titrated to an effective dose of 0.15 mg/kg/d. There was a dramatic reduction in seizure frequency with rapamycin therapy. Further studies are needed to objectively investigate the benefits of rapamycin in tuberous sclerosis complex and to clarify its mechanism of seizure control.

Keywords

tuberous sclerosis; rapamycin; seizures

The article by Zeng and colleagues demonstrating decreased seizure frequency in a mouse model of tuberous sclerosis complex suggests a new and potentially important use for rapamycin in intractable epilepsy.[1] At the University of Texas Tuberous Sclerosis Center, we follow a 10-year-old girl with tuberous sclerosis complex who has been receiving rapamycin for 10 months for seizure control. Tuberous sclerosis complex was diagnosed at 10 months of age following onset of seizures. She was refractory to multiple medications (phenobarbital, carbamazepine, valproate, lamotrigine, tiagabine, gabapentin, leviteracitam, topiramate, and oxcarbamazepine). At 8 years of age, her seizure frequency was 5 to 10 seizures daily. Seizures consisted of right arm paresis with occasional generalization. She was hospitalized for intracranial monitoring and resection of seizure foci. Two tubers were identified as primary areas of seizure onset and were resected without complications. Postoperatively, there was no change in seizure frequency. Within months, our patient had seizure clusters several times weekly. Clusters consisted of 10 to 40 individual episodes of right arm paresis for 10 to 15 seconds. Episodes were not associated with loss of consciousness or with generalization. Seizures were frequent such that right arm paresis persisted between events. Parents were provided an option of further resective surgery or a trial of rapamycin. At 9 years of age, oral rapamycin was initiated at 0.05 mg/kg/d (level 3.8 ng/mL) and was slowly increased. At 0.15 mg/kg/d (level 9.8 ng/mL), seizure clusters stopped; however, 1 to 5 brief seizures (< 2 minutes) continued daily. Right arm strength returned to normal and she stated that she felt “smarter.” Rapamycin was increased to 0.2 mg/kg/d (level 13.7 ng/mL) and she developed skin breakdown, mouth ulcers, and frequent viral infections with no further improvement in seizure frequency. Rapamycin was reduced to 0.15 mg/kg/d without an increase in seizure frequency and adverse effects resolved.

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Pretreatment and posttreatment magnetic resonance brain imaging demonstrated no change in the number or size of her cortical tubers. Throughout the treatment course, the patient received topiramate (6.5 mg/kg/d) and oxcarbamazepine (35 mg/kg/d). Our success with rapamycin in this young girl with tuberous sclerosis complex in reducing her seizures suggests that rapamycin may be a beneficial adjunctive therapy for seizure control in tuberous sclerosis complex. Additionally, the TSC1 knockout mice used by Zeng and colleagues demonstrated decreased seizure frequency when treated early (prior to seizure onset).[1] It remains unclear how rapamycin functions to decrease seizure frequency in tuberous sclerosis complex, but early initiation of rapamycin therapy may modify the course of this disease by decreasing both the frequency and severity of seizures. Further studies are needed to objectively investigate the benefits of rapamycin in tuberous sclerosis complex and to clarify its mechanism of seizure control.

References

1. Zeng LH, Xu L, Gutmann DH, Wong M. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol. 2008; 63:444–453. [PubMed: 18389497]