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Case Report

Rufinamide Adjunctive Therapy Reduced Atypical Absence Seizures on EEG: Case Report and Review of the Literature

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Abstract

Objective

To demonstrate the efficacy and safety of rufinamide as adjunctive therapy for atypical absence epilepsy

Methods

Case Report

Results

A 9 year-old boy presented with episodes of pausing while playing, walking or talking.

He was diagnosed with partial seizures at 3 years based on an outside EEG with focal right temporal epileptiform discharges and started on oxcarbazepine, which caused sedation. He was then diagnosed with atypical absence seizures and switched to ethosuximide with partial response. Adjunctive levetiracetam was ineffective and lamotrigine caused a diffuse rash. Valproic acid caused temper tantrums. Topiramate affected his cognition.

On ethosuximide 250mg twice daily monotherapy he continued to have staring spells.

Birth history was normal without any history of developmental delay. He was academically advanced. Review of systems, family and social history were all negative.

His exam was normal.

His initial EEG on ethosuximide showed numerous 3-4 Hz generalized irregular spike-polyspike complexes mostly activated by photic stimulation.

Rufinamide 400mg twice daily was added to ethosuximide, which decreased seizure duration on EEG by 67% as well as seizure frequency.

Conclusions

This was a case of atypical absence seizures (AAS) where rufinamide was used as a last resort. Rufinamide may be a promising new antiepileptic drug for AAS and possibly for myoclonic absence seizures.

Keywords: Rufinamide; Lennox-Gastaut Syndrome (LGS); Atypical Absence Seizures (AAS)

Introduction

Rufinamide (RUF) is an FDA-approved triazole derivative for adjunctive therapy in Lennox-Gastaut syndrome (LGS) in ages 4 years and above.

Atypical absence seizures (AAS) are generalized seizures associated with slow spike-wave complexes [1].

We present a case of AAS where adjunctive off-label RUF resulted in significant improvement in seizure frequency and duration as demonstrated on EEG.

Materials and Methods:

Case Report

Results

A 9 year-old boy presented with a history of pausing while playing, walking and talking.

He was first diagnosed 6 years ago with partial seizures based on an outside EEG with focal right temporal epileptiform discharges, and was started on oxcarbazepine (OXC), which caused crying and sedation.

He then saw another neurologist who diagnosed him with atypical absence seizures (AAS) and changed his OXC to ethosuximide (ETX), which improved seizure frequency and duration but did not resolve the seizures. Adjunctive levetiracetam (LEV) was ineffective and lamotrigine (LTG) caused a diffuse rash.

He saw a third neurologist who added valproic acid (VPA), which caused severe temper tantrums. Topiramate (TPM) affected his cognition.

Even on ETX 250mg twice daily monotherapy he continued to have staring spells with eyelid fluttering, lasting less than 1second in clusters, at times none for 1-2 weeks. This was once associated with a 1-2 second generalized jerking episode and speech arrest.

He was born full-term weighing 6 pounds 2 ounces. There was a history of benign neonatal jaundice. There was no history of developmental delay. He was academically superior, reading several grades above his age. He would have temper tantrums at home and outside but none at school, which was not related to his seizures, and for which he was seeing Psychiatry.

Past medical history was significant for growth delay with low levels of growth hormone.

Review of systems, family history and social history were all negative.

On exam he was 50.0 inches tall (5^{th} percentile) and weighed 52.6 lbs (25^{th} percentile). Neurological exam was normal. Hyperventilation (HVT) did not activate any episodes.

His initial EEG (Figure 1) on ETX 250mg twice daily monotherapy revealed a total of seventeen 3-4 Hz generalized irregular spike-polyspike complexes, with fifteen activated by intermittent photic stimulation(IPS), lasting a total of 49.6 secs (3.3% of the entire recording). At that time he was having clusters of seizures once every 1-2 weeks.

RUF 400mg twice daily was added to ETX without any side-effects.

His repeat EEG (Figure 2) while on RUF 400mg twice daily and ETX 250mg twice daily 3 months after his first EEG showed total twenty-five runs of 3-4Hz generalized irregular spike-polyspike complexes during post-HVT and activated by IPS, at a total amount 16.4 secs (1.08% of the entire recording) , with the total duration of epileptiform discharges having decreased by 67%. He was having clusters of seizures every 3-4 weeks, showing clinical improvement. RUF levels at a dose of 33mg/kg/day were 19.8 mcg/mL(therapeutic range5-48 mcg/mL) at the time of his repeat EEG. He was lost to follow-up; he had been on RUF for over 6 months without any recurrent seizures or side effects.

Discussion

This was a case of atypical absence seizures (AAS) resistant to ETX monotherapy (at the optimal dose for his age at 20mg/kg/day) and other commonly prescribed antiepileptics, where RUF had to be used as a last resort in order to control the seizures.

Although not fulfilling the classical definition of AAS this case was considered to be such as: A. Polyspike (and not single spike) activity was noted on the EEG. B. IPS rather than HVT activated the epileptiform discharges. However, unlike classic AAS: A. He was very intelligent [2]. B. He was unable to respond at all during the episodes. C. He did not have LGS. D. The frequency of the epileptiform discharges was 4Hz and not slower. He had only a couple of episodes of myoclonic jerks, making the diagnosis of myoclonic absence epilepsy less likely. Absence seizures with polyspike-onset 3-Hz generalized spike wave complexes (as in this case) suggest an intermediary form of IGE that may be drug resistant [3].

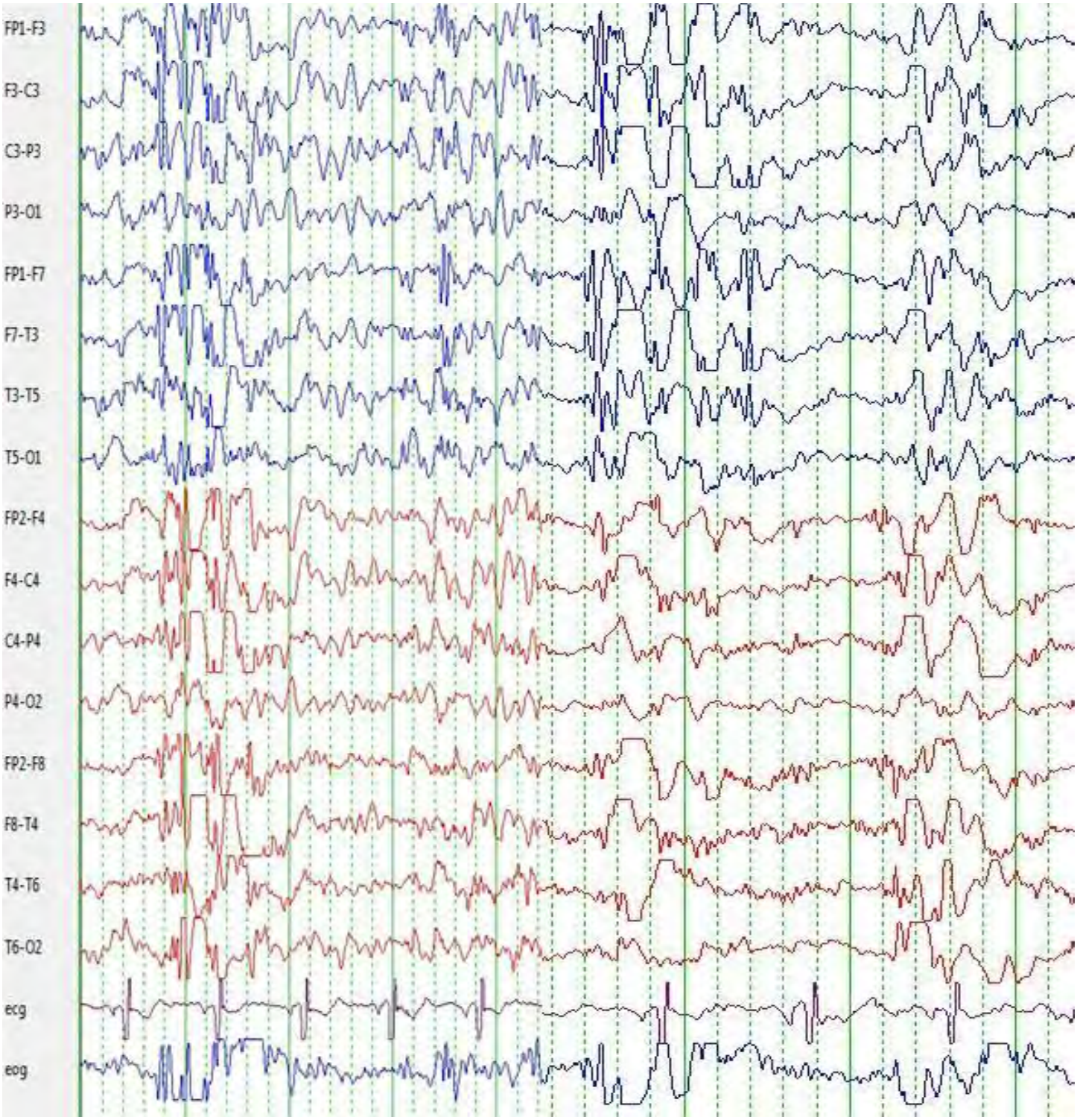

Figure 1. Bipolar montage of baseline EEG consisting of 3-4 Hz generalized irregular spike-polyspike complexes, mostly activated by IPS, at a total of 49.6 secs (3.3% of the entire recording), while on ETX 250mg twice daily as monotherapy.

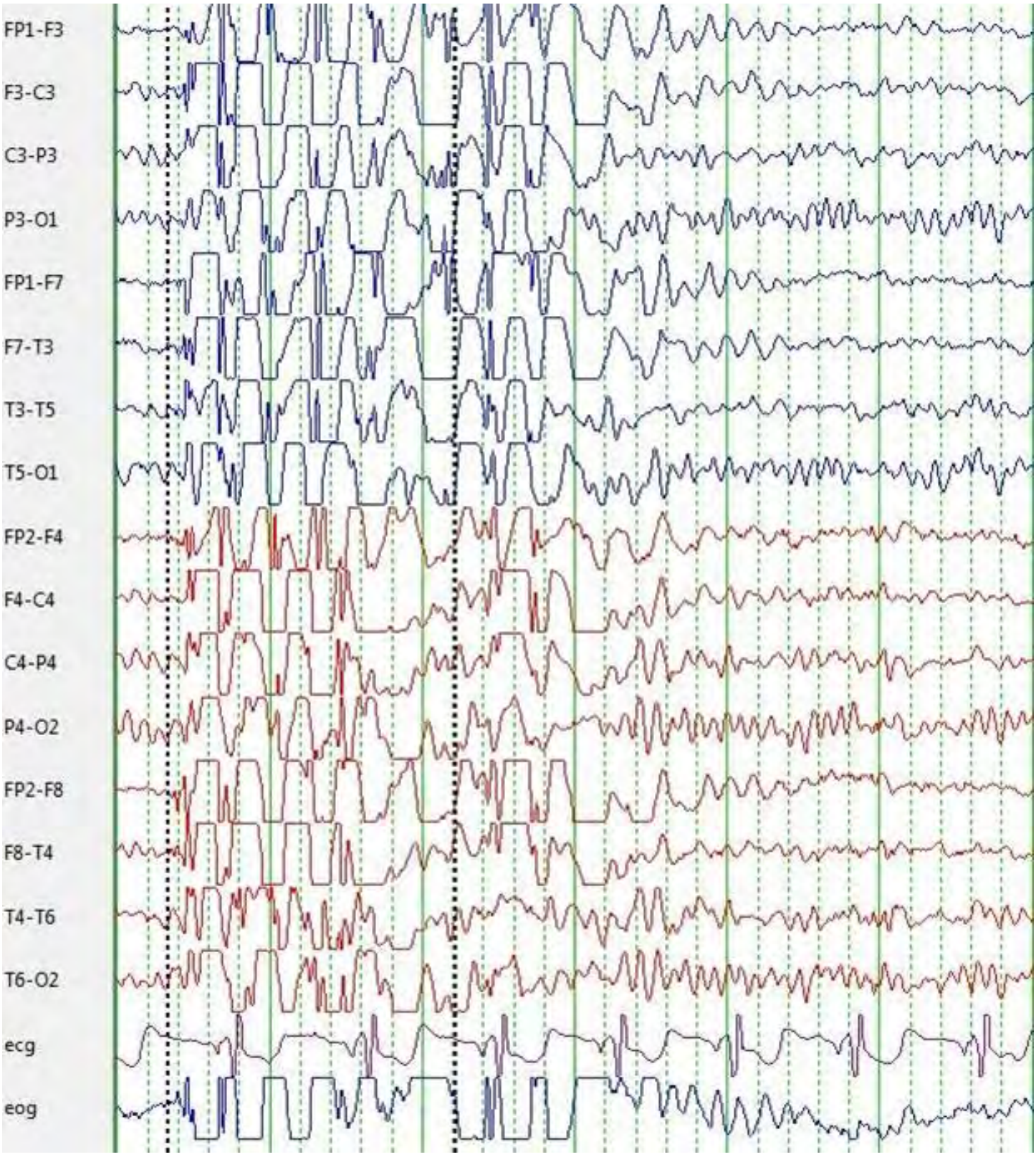

Figure 2. Bipolar montage of repeat EEG consisting of 3-4Hz generalized irregular spike-polyspike complexes activated by IPS, at a total of 16.4 secs (1.08% of total recording) while on ETX 250mg twice daily and RUF 400mg twice daily. The total duration had decreased by 67%.

RUF is a triazole derivative which was FDA approved in 2008 for the adjunctive treatment of seizures associated with LGS in children 4 years and older and adults.

RUF inhibits Nav1.1 activation [4]. Although there are no reports of Nav1.1 mutations causing AAS or CAS, NaV1.1 mutations with complete loss-of-function cause severe myoclonic epilepsy of infancy (SMEI) and missense mutations cause generalized epilepsy with febrile seizures plus (GEFS+) [5]. A NaV1.6 mutation leading to loss of function was found to cause absence seizures in mice [6].

Currently, evidence-based guidelines for managing AAS are lacking. VPA and ETX are classically the preferred treatments for AAS, both of which this patient had tried.

Here we were able to demonstrate the efficacy of RUF by quantifying the total duration of epileptiform discharges on a 30 minute outpatient EEG and objectively demonstrate a decrease in the total duration by 67% at a dose of 33mg/kg/day. RUF at a maintenance dose of 45 mg/kg/day results in plasma concentrations ranging from 5-48 mcg/mL [7]. Although we had not quite achieved the target dose of 45mg/kg/day (as the patient was lost to follow-up), even at a dose of 33mg/kg/day within therapeutic range we were able to significantly decrease the total duration of epileptiform discharges. Compared with LGS, we were able to achieve a decrease in seizure frequency by 50% at far lower levels [8].

Our patient had tolerated RUF well; he could not tolerate OXC, VPA, LTG, or TPM, and LEV was ineffective.

RUF appears to be the most promising new antiepileptic drug for AAS and possibly for myoclonic absences [9]. A12-week randomized, placebo-controlled study involving 139 patients with LGS revealed that the frequency of AAS had decreased by 50.6% in the RUF group versus 29.8% in the placebo group [10]. RUF might also be effective in treating other forms of epilepsy [11-13]. A retrospective analysis involving 3 cases of refractory epilepsy with myoclonic absences reported the efficacy of RUF as adjunctive therapy [14]. Another retrospective analysis reported its efficacy in migrating partial epilepsy of infancy [15]. There was also a report of RUF controlling seizures in methyl malonic aciduria [16]. Large-scale, randomized, placebo-controlled studies are in need to demonstrate the efficacy and safety of RUF as adjunctive therapy in AAS.

In conclusion, our case suggests that RUF may be a safe and effective option for adjunctive therapy in AAS.

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