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# Low-dose fenfluramine as an effective treatment option for 'atypical' Dravet syndrome

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ABSTRACT

Dravet syndrome (DS) is characterized by recurrent convulsive seizures, including status epilepticus, and intellectual disability as a comorbidity. Seizures associated with DS are commonly resistant to antiseizure medications. Typical features of DS are recurrent episodes of status epilepticus, the presence of genetic mutations, and no abnormal magnetic resonance imaging (MRI) findings. Here, we report a rare case of DS in a 14-year-old girl who was negative for genetic mutations, had experienced status epilepticus only once, and had abnormal findings on brain MRI. Although our patient's case features are atypical of DS, they do not contradict the diagnostic criteria. Despite the difficulty in diagnosing DS because of the negative genetic testing results, we started our patient on fenfluramine (FFA). Long-term treatment with low-dose FFA effectively controlled our patient's seizures and resulted in cognitive and functional improvements.

## 1. Introduction

Dravet syndrome (DS) is a rare form of epilepsy characterized by recurrent convulsive seizures, including status epilepticus, and mild to moderate intellectual disability as a comorbidity [1]. Individuals with DS often have seizures that are resistant to anticonvulsant medications [2]. Tonic-clonic or clonic febrile seizures generally begin in infancy, although infants with DS usually exhibit typical development until around 1 year of age [3]. Status epilepticus is more frequent in children younger than school age [3]. Beyond the age of 5 years, the frequency of seizures starts to decrease, but status epilepticus and unexpected death from DS-related epilepsy result in a higher mortality rate than among individuals with other types of epilepsy [4]. Further, the frequency of seizures results in a significant burden for those with DS and drives cognitive dysfunction [5]. As such, controlling seizures in those with DS is imperative.

Since 2020, increased attention has focused on the use of fenfluramine (FFA), which was once marketed as an appetite suppressant [6], for the treatment of seizures in DS. Here, we present an atypical case of DS in a 14-year-old girl in whom FFA was remarkably effective.

## 2. Case presentation

In this case, the patient's epilepsy started with an afebrile convulsion at 3 months of age. Thereafter, convulsive seizures were easily provoked by high fever and were resistant to antiseizure medications. The patient experienced convulsive status epilepticus (lasting ~ 30 min) only once at 11 months of age. The patient did not exhibit any significant developmental delays in infancy, with delays only recognized after 1 year of age. Specifically, the patient took her first steps at the age of 2 years and 3 months and started to clearly use single words at the age of 3 years and 11 months. The patient experienced only febrile or afebrile generalized tonic-clonic seizures (GTCS) and did not develop any other seizure types.

Brain magnetic resonance imaging (MRI) at 1 year of age revealed bilateral multiple periventricular nodular heterotopia (PVNH) without cortical heterotopia (Fig. 1). The patient experienced an episode of acute encephalopathy at 5 years of age, which left her with cognitive and

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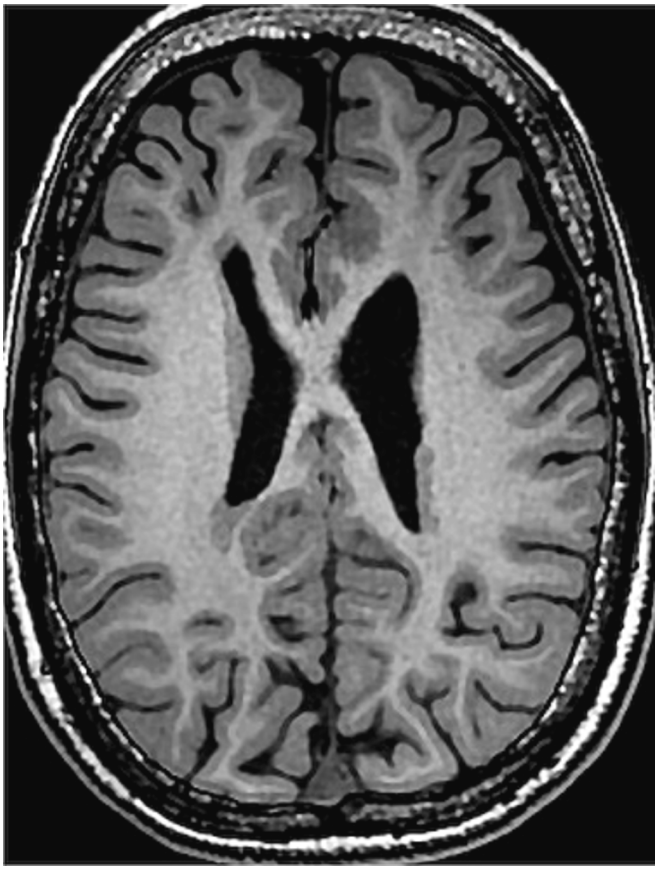

**Fig. 1.** Magnetic resonance imaging using spoiled gradient echo of the patient at 1 year of age revealed bilateral multiple periventricular nodular heterotopia.

motor regression. The patient lost the ability to communicate and required support to maintain a standing position. No mutations were detected in the sodium voltage-gated channel alpha subunit 1 (*SCN1A*), protocadherin 19 (*PCDH19*), and filamin genes at 5 years of age. Different medications were tried to control the patient's seizures, including valproic acid (VPA), carbamazepine, phenobarbital, zonisamide, levetiracetam, perampanel, clobazam (CLB), clonazepam, nitrazepam, gabapentin, topiramate (TPM), stiripentol, and potassium bromide (KBr), but all were ineffective.

At her first visit to the National Epilepsy Center at 11 years of age, the patient was having 20 seizures per week and was being treated with KBr 19 mg/kg/day, VPA 19 mg/kg/day, CLB 0.2 mg/kg/day, lamotrigine (LTG) 1.5 mg/kg/day, and TPM 8.6 mg/kg/day. An electroencephalography (EEG) sleep record prior to the initiation of FFA revealed a burst of bilateral frontal dominant sharp waves (Fig. 2A). We considered a diagnosis of DS due to the presence of intractable convulsive seizures that were easily provoked by high fever. Because discontinuation of LTG did not improve the seizures, we started treatment with FFA 0.2 mg/kg/day. The patient was seizure free for 6 weeks, but experienced somnolence. Decreasing the dose of FFA to 0.12 mg/kg/day improved her somnolence, and the patient remained seizure free for 3 months. Treatment with low-dose FFA (0.12 mg/kg/day) for 7 months markedly improved the EEG sleep record (Fig. 2B). Subsequently, KBr was gradually discontinued, after which the patient regained the ability to communicate verbally and was able to walk alone.

After a 1-year seizure-free period, the patient experienced a relapse of convulsive seizures. The dose of FFA was increased to 0.15 mg/kg/day, and although the seizures occurred monthly, they were much weaker than prior to the introduction of FFA. After starting on FFA, the patient's GTCS lasting 1 min were superseded by a tonic seizure lasting 10 s, followed by several clonic jerks. The patient experienced no adverse events on FFA except for transient diarrhea and somnolence. A cardiac ultrasound examination 6 months after initiating FFA was normal, and low-dose (0.12 mg/kg/day) FFA was not associated with any adverse events.

## 3. Discussion

In our patient, MRI revealed PVNH. In DS, neuroradiological studies usually do not show specific abnormal findings [7], and PVNH is rarely reported [8]. Furthermore, there is usually no correlation between the presence of MRI abnormalities and either the age at seizure onset or seizure duration [9]. In our patient, PVNH was not considered to be the cause of epilepsy given the lack of clinico-electrical correlation. However, Guerrini et al [9] previously reported abnormal findings related to DS usually only observed in patients without *SCN1A* mutations. Although it is difficult to completely rule out PVNH as the cause of epilepsy in our patient, her seizures were easily provoked by a high fever, which is a characteristic feature of DS. The clinical features of our patient were consistent with those of DS, except for the presence of PVNH and the absence of an *SCN1A* mutation, and so we consider this to be a case of atypical DS.

Based on the 2022 International League Against Epilepsy (ILAE) classification and definition of epilepsy syndromes [10], episodes of statues epilepticus are common in DS before 5 years of age. Although recurrent episodes of status epilepticus are common in DS [3], our patient experienced only one episode of status epilepticus (at 11 months of age), which is atypical for DS. However, recurrent episodes of status epilepticus are not mandatory for a diagnosis of DS [10]; rather, recurrent intractable convulsive seizures that are easily provoked by fever are more important for the diagnosis of DS [11,12], and our patient met this criterion.

No gene mutations were detected in our patient. It has been reported that only 20 % of patients with DS are negative for gene mutations, and that 80–85 % of patients with DS have a pathogenic variant in the *SCN1A* gene [13]. However, a diagnosis of DS should not be made on the basis of positive gene mutation test results, and, conversely, a diagnosis of DS should not be ruled out in the absence of gene mutations [14]. Relying on the presence of gene mutations to diagnose DS could lead to delays in precise treatment and a poor clinical course for patients with DS.

Overall, the diagnosis of DS in our patient was challenging due to the presence of abnormal findings on brain MRI, negative genetic testing results, and the lack of multiple episodes of status epilepticus, all of which could be considered 'atypical' features of DS. However, these features do not contradict the 2022 ILAE diagnostic criteria for DS, in which a positive gene mutation result is classified as 'optional' for the diagnosis of DS [10].

We diagnosed our patient as having DS and decided to start her on FFA, which resulted in good clinical outcomes with a long seizure-free period, as well as improvements in cognitive and motor function associated with the discontinuation of ineffective medications, such as LTG, KBr, and TPM. DS can be classified as a developmental and epileptic encephalopathy [3]. Because seizure frequency decreased and there were marked improvements in EEG findings after initiating FFA, we consider that our patient also experienced improvements in cognitive and functional aspects after treatment for epileptic encephalopathy.

## 4. Conclusion

We propose that FFA is an effective treatment for DS with atypical features in patients experiencing recurrent seizures that are easily provoked by high fever from infancy, together with intellectual disabilities, regardless of the presence of genetic mutations or multiple episodes of status epilepticus. Furthermore, this case demonstrates that a differential diagnosis of DS should be considered in patients with both intractable recurrent convulsive seizures that are easily provoked by fever and

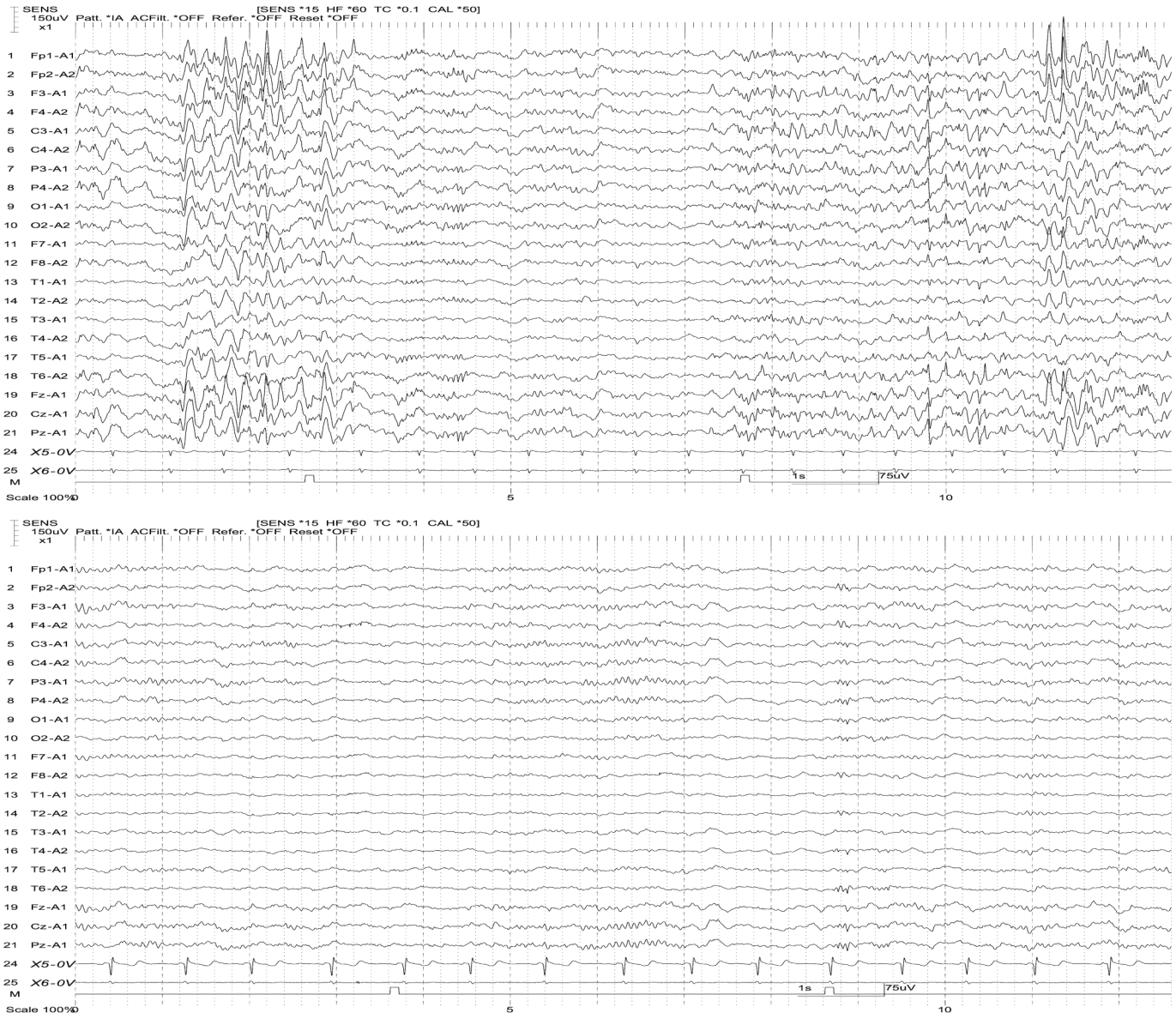


**Fig. 2. (A)** An electroencephalograph (EEG) sleep record prior to the initiation of fenfluramine (FFA) revealed a burst of bilateral frontal dominant sharp waves. **(B)** The administration of low-dose (0.12 mg/kg/day) FFA for 7 months led to a marked improvement in the EEG sleep record.

intellectual disabilities, even if other clinical features are atypical of DS, and treatment with FFA initiated. A comprehensive diagnosis is important in patients with epilepsy syndromes.

## Ethical statement

Ethical review was waived for this study due to its case report nature, and informed consent was obtained from the parents.

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## CRediT authorship contribution statement

**Akihiro Iguchi:** Writing – review & editing, Writing – original draft, Validation. **Tokito Yamaguchi:** Validation. **Tomona Yabe:** Validation. **Mitsuhiro Miyashita:** Validation. **Satoshi Mizutani:** Validation. **Hideyuki Otani:** Validation. **Rie Miyata:** Validation. **Katsumi Imai:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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