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Case Report

Seizure reduction with fluoxetine in an adult woman with Dravet syndrome

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ABSTRACT

An adult woman with Dravet syndrome (documented SCN1A mutation) experienced a marked reduction in seizures when treated with the selective serotonin reuptake inhibitor (SSRI) fluoxetine. The seizure reduction may be partly due to reductions associated with aging in patients with Dravet syndrome, but it appears to be due, at least in part, to fluoxetine. A prior preliminary study reported that fenfluramine reduces seizures in patients with Dravet syndrome. Fenfluramine may produce this effect by increasing serotonin brain levels, and SSRIs have been found to possess antiepileptic properties in animal models of epilepsy. Given the known cardiac risks of fenfluramine, randomized clinical trials with SSRIs should be considered in Dravet syndrome and other types of epilepsy.

1. Introduction

Dravet syndrome is an epileptic encephalopathy, which was first described in 1978 [1,2]. It is a spectrum of conditions with variability in severity and manifestations but usually with catastrophic consequences [3].

1.1. Etiology

Mutations in the voltage-gated sodium-channel gene alpha subunit (SCN1A) were discovered in an epileptic syndrome called genetic epilepsy with febrile seizures plus (GEF+) including some patients with severe myoclonic epilepsy of infancy (SMEI) in GEF+ families [4–6]. Later, new SCN1A mutations were found in nonfamilial SMEI [7]; these mutations were de novo and more severe than those associated with GEF+ [8]. Because some patients with the epileptic encephalopathy do not exhibit myoclonus, the disorder is now known as Dravet syndrome. Approximately 90% of patients with Dravet syndrome have de novo mutations, about 75% of patients with Dravet syndrome have mutations in the gene encoding SCN1A, and over 300 SCN1A mutations on chromosome 2q24 have been found [8,9]. Other genes implicated in Dravet syndrome include PCDH19, GABRG2, and SCN1B [8].

Animal models exhibit the characteristic temperature/age dependent seizures seen in humans, and there is a 50% reduction in sodium current in heterozygous SCN1A mutations [10]. Since the SCN1A protein is expressed predominately in GABAergic interneurons as opposed to excitatory pyramidal neurons, Dravet syndrome is considered a genetic dysfunction of inhibitory interneurons [8,11].

1.2. Clinical manifestations

Onset is typically in the first year of life in a previously healthy infant who experiences a seizure associated with fever, vaccination, or illness [8]. Initial seizures are generalized or hemiclonic, and the first seizure may be status epilepticus. Over the next few years, other seizure types usually develop, which may include atypical absence, focal (with impaired consciousness), myoclonic, atonic, and tonic seizures and convulsive or nonconvulsive status. Seizures may be triggered by fever, fatigue, photosensitivity, or excitement [2]. By the age of 2 years, developmental delay is usually apparent. Deterioration occurs from ages 1 to 4 years with the occurrence of psychomotor, behavioral, and gait abnormalities [2]. After age 5, convulsive seizures usually decrease and may occur mainly in sleep [2]. Cognitive and behavioral problems stabilize and may improve to a degree, but at least half of patients remain severely impaired. Magnetic resonance imaging shows only diffuse atrophy, and EEG may have diffuse slowing with generalized spike and polyspike and wave discharges and/or multifocal epileptiform discharges [8]. The seizures are typically medically resistant. Carbamazepine, lamotrigine,

Abbreviations: AED, antiepileptic drug; SSRI, selective serotonin reuptake inhibitor; SCN1A, sodium-channel gene alpha subunit; SMEI, severe myoclonic epilepsy of infancy; GEF+, genetic epilepsy with febrile seizures plus.

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and phenytoin may exacerbate seizures. Valproate, benzodiazepines, stiripentol, and topiramate are the most effective antiepileptic drugs. However, seizures persist into adulthood [8]. Mortality is about 15% by adulthood in patients with Dravet syndrome [8].

2. Case report

The case report described here was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). DL is a 27-year-old woman with Dravet syndrome. She has a confirmed SCN1A mutation with deletion of 1 bp of C nucleotide position 1650, codon 550. Her first seizure occurred at age 4 months after a diphtheria–pertussis–tetanus vaccination without fever; it consisted of some left-arm jerks. She had her first convulsion at age 6 months and her first episode of status epilepticus at age 3 years after which her development was noted to be distinctly abnormal. Over the years, DL suffered from multiple seizure types including generalized tonic–clonic, focal (with impaired consciousness), and myoclonic seizures and atonic drop attacks. Seizures were increased with fever and later in a catamenial pattern. Her seizures failed to improve with multiple antiepileptic drugs including carbamazepine, clobazam, clonazepam, clorazepate, felbamate, lamotrigine, levetiracetam, lorazepam, phenobarbital, phenytoin, primidone, retigabine, stiripentol, tiagabine, topiramate, valproate, and zonisamide. A strict ketogenic diet and vagal nerve stimulation also failed to improve her seizures.

Magnetic resonance imaging showed only diffuse atrophy. Electroencephalograms and video-EEGs revealed multifocal spikes and polyspikes interictally, and recorded generalized tonic–clonic seizures had ictal onsets with diffuse decrement. Her genetic diagnosis was made at age 21 years.

In late July 2009, DL was started on fluoxetine 20 mg daily in an attempt to reduce stereotypic behaviors characterized as vigorous back-and-forth head shaking, which was sometimes associated with facial grimace and raising of her legs into a flexed position. These behaviors occurred multiple times per day but did not occur out of sleep. The family thought that they could sometimes be interrupted with distraction. At the time, DL's medications included felbamate (2400 mg/day), levetiracetam (1000 mg/day; higher dosages were ineffective and caused behavioral problems), diazepam PR PRN, lorazepam PO PRN, fexofenadine PRN, medroxyprogesterone, polyethylene glycol, melatonin, and multivitamins. Her last prior medication change had been tapering and then stopping of stiripentol in May 2009, which did not cause any worsening of her seizures on withdrawal.

Fluoxetine therapy was effective in markedly reducing the stereotypic behaviors, but, surprisingly, it was also associated with a marked reduction in seizures. In the months preceding fluoxetine in that year, DL had an average of 8–10 seizures per month. In the remaining months of that year after initiation of fluoxetine, DL's seizure frequency dropped to 3–4 per month, and the seizures were less severe. This reduction in seizures has been maintained, and the seizures even improved over subsequent years without any other changes in antiepileptic drugs. Her seizures were predominantly generalized tonic–clonic seizures in recent years. Now, they are rare, brief, and usually nocturnal. Her behavior and cognitive function have also had modest improvements (see Table 1 for annual seizure rates).

Table 1
Total annual seizures for DL. Note that fluoxetine was initiated in the later half of 2009.

Year	Total # of seizures
2007	116
2008	95
2009	93
2010	37
2011	16
2012	12
2013	4

3. Discussion

The observed reduction in seizure could be due to the natural reduction in seizures in patients with Dravet syndrome that occurs with aging [2]. However, fluoxetine was begun at age 24 years, and the seizure reduction typically occurs before that age. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). Recently, a preliminary study showed remarkable efficacy for fenfluramine in reducing seizures in patients with Dravet syndrome [12]. Fenfluramine increases serotonin levels via inhibition of serotonin uptake and disruption of serotonin of vesicular storage [12].

Several investigations suggest that serotonin possesses antiepileptic properties [13]. For example, SSRIs increase extracellular 5-HT, which inhibits focal and generalized seizures in several animal models of generalized epilepsy and focal epilepsy [14–16]. Activation of 5HT1A receptors can result in membrane hyperpolarizing associated with increased potassium conductance [17,18], and stimulation of 5HT1A receptors in the thalamus can increase GABA release, reducing excitation in an animal model [19]. Further, 5HT2C agonists prevent seizures, and 5HT2C antagonists lower seizure threshold in both focal and generalized models of epilepsy [20]. In humans, three open trials with SSRIs have also suggested possible antiepileptic effects [21–23]. Specifically in regard to fluoxetine, an open trial of 17 patients with focal epilepsy followed over a mean of 14 months reported seizure freedom in 6 patients and decreased seizure frequency by 30% in the other 11 patients [23]. Thus, the observed response to fluoxetine in DL may be due to its serotonin effects.

4. Conclusions

This case report suggests that the SSRI fluoxetine may have efficacy in reducing seizures in Dravet syndrome. The finding is consistent with the preliminary findings of antiseizure efficacy for fenfluramine, another agent with serotonergic effects. In addition, several investigations in animals suggest that serotonin agents possess antiepileptic properties. Given the potential adverse cardiac effects of fenfluramine, randomized clinical trials of other serotoninergic agents like fluoxetine should be considered in patients with Dravet syndrome and other types of epilepsy.

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Conflicts of interest

Dr. Meador reports no financial conflicts of interest in relation to this publication.

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