Dravet Syndrome

Dravet syndrome is a rare, severe, therapy-resistant epileptic syndrome first described by Charlotte Dravet in 1978. It affects an estimated 1 in 20,000 to 40,000 children.[1][2]

- Children with Dravet syndrome are developmentally normal infants at the time of first occurrence of recurrent seizures which are usually provoked by a fever.[3]
- Diagnosis of Dravet syndrome is based on clinical presentation including the child’s age at seizure onset, evolution of seizure types, electroencephalographic (EEG) features, and developmental course.[4]
- Patients with Dravet syndrome most commonly present with seizures before 7 months:
  - The seizures have longer duration (10+ minutes), occur more frequently (often ≥5 in infancy), and consist of hemiconvulsions, myoclonic seizures, or focal seizures.
  - Around 2 years of age, developmental delay becomes evident, and multiple other therapy-resistant seizure types begin to appear.
- Approximately 70% of patients have genetic evidence of Dravet syndrome.[5]
  - The most common mutation is in the SCN1A gene, which encodes for a subunit of the voltage-gated sodium channel β1.1

Treatment of Dravet Syndrome

- Dravet syndrome is resistant to common epileptic drugs.
- Rational adequate maintenance therapy is initiated using antiepileptic drugs (AEDs) with avoidance of specific sodium channel-blocking agents such as lamotrigine, carbamazepine, and phenytoin, which aggravate symptoms of Dravet syndrome.
- Anticonvulsants that have been useful for chronic seizure management in Dravet syndrome include clobazam (CLB), clonazepam, levetiracetam, stiripentol (STP), topiramate, and valproic acid (VPA).[6]
  - STP has been effective in some patients with Dravet syndrome when used in combination with VPA and CLB, STP is not FDA approved.

Fenfluramine and Epilepsy

- Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) was originally developed as an appetite suppressant and is believed to act through serotonergic mechanisms.[7]
- Early preclinical experiments by Bonnycastle et al. suggested that elevated serotonin in the CNS modulates epilepsy.[8]
- Approximately 75% of patients have genetic evidence of Dravet syndrome[9]

History of the Use of Low-dose Fenfluramine in Pediatric Epilepsy

1978

Charlotte Dravet

1984

Henri Gastaut, “Efficacy of Fenfluramine for the Treatment of Compulsive Behavior Disorders in Psychiatric Children”

1985

Henri Gastaut and Benjamin G. Zifkin, “Antiepileptic Effects of Fenfluramine: Pilot Study” in Annals of Neurology

1987

Jean Aicardi and Henri Gastaut, “Treatment of Self-induced Photсенsitive Epilepsy with Fenfluramine” in the New England Journal of Medicine

REFERENCES


DISCLOSURES

Presented as part of the Zogenix Scientific Exhibit during the 70th Annual Meeting of the American Epilepsy Society, December 2-6, 2016, Houston, TX.
A 5.5-year-old boy developed excessive syncopal attacks associated with self-induced tonic-clonic seizures. At 1 year, the patient was treated with fenfluramine (10 mg, twice daily), VPA, and carbamazepine with a dramatic reduction in seizure frequency to 2-3 seizures/24 hours and there was marked improvement in his behavior.

This retrospective study reports the clinical outcome of 12 patients with Dravet syndrome after the addition of fenfluramine to their current treatment. Patients were seen twice a year and treatment efficacy, based on an individualized seizure diary, AED changes, and side effects were noted. Patients underwent a full clinical examination, a yearly cardiac examination, and routine blood examination. A total of 7 out of 10 patients were seizure free for at least a year by the time of the last visit; 1 patient had a 75% reduction in seizure frequency.

In a letter to the editor, Casara and Boel follow up their previous study with an additional 22 patients (11 boys, 11 girls) with severe tonic-clonic seizures before the add-on therapy of fenfluramine (dose between 0.25 and 1 mg/kg/day).

The apneic attacks disappeared within 48 hours and there was marked improvement in behavior.

Current and Upcoming Clinical Trials

- In Belgium, the prospective clinical study of patients with Dravet syndrome treated with low-dose fenfluramine was initiated in 2010 and is ongoing.
- In the United States, there are several available, active, or recruiting clinical trials in Dravet syndrome investigating various treatments such as TIP and cannabidiol.
- Two identical clinical trials investigating the use of 2 fixed doses of fenfluramine hydrochloride and solution as adjunctive therapy in children and young adults with Dravet syndrome and sponsored by Boehringer Ingelheim are currently underway in the United States and Canada and in a multinational study primarily in Europe.

Table 1: Summary of Studies of Fenfluramine in Epilepsy

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study Type</th>
<th>N</th>
<th>Age (years)</th>
<th>Primary Diagnoses</th>
<th>Fenfluramine dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemens1</td>
<td>Case report</td>
<td>1</td>
<td>11</td>
<td>Seizure-free during add-on treatment for Dravet syndrome</td>
<td>0.5–1 mg/kg/day</td>
<td>100% reduction in seizure frequency in 6 patients</td>
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<td>0–11</td>
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