Child Neurology Open
1-3

DOI: 10.1177/2329048X211050711
journals.sagepub.com/home/cno
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Long-term Efficacy of Perampanel in a Child with Dravet Syndrome

Eulàlia Turón-Viñas[1], Asunción Díaz-Gómez[1], Elisabet Coca[1], Lucía Dougherty[1], Carlos Ruiz[1], and Susana Boronat[1]

Abstract

Dravet syndrome is a genetic developmental and epileptic encephalopathy (DEE) mostly due to mutations in SCN1A gene. Perampanel is a selective and non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. There is increasing experience in the use of perampanel in this syndrome; however, there is still a lack of evidence of sustained benefit years after the beginning of the treatment.

We report a twelve-year-old girl who was diagnosed with Dravet Syndrome when she was 2 years old and has been on perampanel since she was 7. Her genetic test showed a de novo previously described heterozygous SCN1A mutation in the 24th exon (c.4547C>A, p.Ser1516*). She received previous antiseizure drug combinations with little benefit. When perampanel was started, there was a complete resolution of her spontaneous seizures that has continued five years later. More studies are needed to investigate if there is an association between this excellent response and the genotype of our patient.

Keywords

Dravet Syndrome, perampanel, children, case report.

Received March 9, 2021. Received revised May 12, 2021. Accepted for publication September 13, 2021.

Introduction

Dravet syndrome is a genetic developmental and epileptic encephalopathy (DEE) mostly due to mutations in SCN1A gene.[1] Several antiseizure drugs (ASD) have been tested in patients with this syndrome, with only few of them showing some benefit. Previous reports have shown that the combination of valproate, clobazam and stiripentol are effective in reducing the frequency of seizures in patients diagnosed of Dravet syndrome.[2] Ketogenic diet also reduces seizure frequency and duration in DEE.[3] Recently, some new drugs, like cannabidiol, especially in addition to clobazam, and fenfluramine have proved to be also effective,[4,5] although they are still not commercialised in some countries. Besides, there is still little evidence of perampanel benefits in Dravet Syndrome, especially long-term benefits. We present a patient with Dravet syndrome and excellent long-term response to perampanel.

Case

Our patient is a 12-year-old girl who was diagnosed of Dravet syndrome at 2 years of age. Her first seizures were bilateral tonic-clonic and occurred when she was 7 months old during a febrile illness. She later developed febrile generalized and unilateral seizures, and suffered two status epilepticus before she was 2 years old. At this age, she also presented with myoclonic seizures and monthly focal motor afebrile seizures. A psychomotor delay became evident at this age. Genetic test performed at 2 years of age revealed a *de novo* heterozygous SCN1A mutation in the 24th exon (c.4547C>A, p.Ser1516*), previously described as pathogenic in other patients with Dravet syndrome. Another mutation, found in SCN2A gene (c.1329A>C, p.Glu43Asp), was ruled out because it was inherited from her healthy mother.

From 2 to 6 years of age there was a dramatic increase in her seizure frequency. At school, she suffered from daily reflex myoclonic seizures triggered by fixation on patterns (plaid

[1]Child Neurology Unit, Hospital Sant Pau, Barcelona, Spain

Corresponding Author:
Eulàlia Turón-Viñas, MD, PhD. Child Neurology Unit, Pediatrics Department. Hospital Sant Pau, Barcelona (Spain).
Email: eturon@santpau.cat

fabric), mostly by staring to her friends' pinafores, and myoclonic jerks appeared during the bath time; she also presented with weekly obtundation status and daily atypical absences with myoclonia. Although suspected, no photosensitivity was ever demonstrated on EEGs. During this period, many ASD combinations were trialed, with only slight transient improvement with few of them (valproic acid alone or together with levetiracetam, clobazam, clonazepam, topiramate; topiramate with clobazam; clobazam alone). When she was 7 years old, perampanel was added to her previous treatment with clobazam and valproate, starting at a dose of 2mg and increasing to a maximum of 4mg 2 weeks later. She experienced a complete resolution of the spontaneous seizures from the second week of treatment and no side effects were reported. Due to this excellent response, no higher dose was tested. She is now 12 years old and she only suffers from seizures during febrile infections and water immersion, therefore an increased dose of clonazepam is administered in these situations. She has also shown a slight improvement on her behaviour that could be attributed to the decrease in seizure frequency.

Discussion

Dravet syndrome is a severe DEE characterized by multiple seizure types.[1] It usually begins with complex febrile seizures in young infants with other types of seizures developing later, being myoclonic and hemiclonic seizures, obtundation status and reflex seizures the most typical ones. Mutations in the SCN1A gene are found in up to 80% of patients with Dravet syndrome. A genotype-phenotype relation has been proposed, by which truncating mutations, like the one found in our patient, could be found in patients with early onset of seizures and worse cognitive outcomes.[6–9] SCN1A encodes the alpha-subunit of neuronal voltage gated sodium ion channel, type1 (NaV 1.1), which is primarily expressed in neuronal cells in the central nervous system.[10] A loss of its function seems to affect inhibitory GABAergic pathways and lead to epilepsy.

Perampanel is a selective and noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist.[11] The AMPA receptor is a subtype of glutamate receptor and plays a role in excitatory postsynaptic potentials.

Perampanel has proved to be effective in both focal and generalized seizures, and has been used in children and adolescents with refractory epilepsy. In some previous reports, few patients with Dravet syndrome were included,[12–17] but only 3 of these patients were under 7 years of age. Besides, follow-up on previous reports was no longer than 12 months; Chang demonstrates that, contrary to other etiologies, patients with Dravet syndrome who respond to perampanel remained stable up to 12 months after its initiation,[12] but there is a lack of studies with longer follow-up.

Efficacy studies show that some patients can improve drastically with perampanel, even obtain a complete remission of their seizures, while other patients show no improvement or even deterioration.[13] Besides, perampanel seems not to target a specific seizure type but to be effective in all seizure types, in a "all-or-nothing" fashion, when effective.[13] The efficacy of perampanel has also been described as disease-specific in Dravet syndrome.[12] An impaired GABA inhibition secondary to AMPA receptor-mediated excitotoxicity has been proved in Dravet syndrome, which leads to epilepsy development. In this situation, an AMPAR antagonist may attenuate this impaired GABAergic transmission and therefore help control seizures. Besides, Ishikawa reported a newborn with an early myoclonic epilepsy with a SCN1A mutation with excellent response to perampanel, suggesting that this effect could be also SCN1A-mutation-specific.[18] However, up to 33% of patients in the previous reports showed no benefit or even deterioration with perampanel in patients with mutations in SCN1A.[12–17] More studies are needed to investigate if there is an association between the response to certain drugs as perampanel and the patient's genotype.

Another interesting unanswered question is whether the efficacy in our patient, and also in previous reports, is due to perampanel alone or in combination to other ASD. Our patient was being treated with valproate and clobazam, suffering from frequent seizures, and she immediately experienced an excellent response after adding perampanel. Although there seems to be a clear relation to perampanel initiation, we cannot rule out a synergistic effect of the three drugs. Previous reports does not analyze the effect of perampanel on patients with Dravet syndrome in combination with other treatments.[13,15]

To conclude, we present a 12-year-old patient with Dravet syndrome who has been under treatment with perampanel for the last 5 years with a complete control of her spontaneous seizures. To the best of our knowledge this is the longest follow-up of perampanel on Dravet syndrome reported to date.

Acknowledgments

This work was supported by the Dravet Syndrome Foundation Spain.

Author Contributions

ET and AD conceived the idea. ET wrote the draft and proof with suport from AD, EC, LD and CR. SB helped supervise the project.

Ethics and Patient Consent

Our institution does not require ethical approval for reporting individual cases. Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

ORCID iD

Eulàlia Turón-Viñas https://orcid.org/0000-0001-6171-0282

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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