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Case Report

Severe myoclonic epilepsy of infancy: Seizure reduction during adjunctive eslicarbazepine in two cases☆

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ABSTRACT

Objective: The aim of this study was to preliminarily determine, in a short open study, the effectiveness of eslicarbazepine acetate (ESL) in two patients with severe myoclonic epilepsy of infancy (SMEI).
Methods: We report on a 17-year-old Italian boy and a 21-year-old Italian girl with SMEI and a severe clinical outcome, in whom we identified two mutations (5053del AA fs1685X1691 and 931G>T E311X) in the alpha subunit of the neuronal sodium channel SCN1A gene. No drug treatment, including carbamazepine, phenobarbital, valproate, vigabatrin, clonazepam, lamotrigine, phenytoin, nitrazepam, felbamate, zonisamide, or lacosamide, had proven effective, and in the first patient, a VNS pacemaker implantation was tried. The patients suffered from severe and profound mental retardation, respectively. Seizures started in the first year of their life. The last EEGs showed slow background activity and paroxysmal activity in the frontal regions in the boy and slow background activity and paroxysmal activity in the temporooccipital regions with secondary diffusion in the girl.
Results: We observed in both patients after a few weeks from the start of ESL (at a dosage of 800 mg once daily) an important reduction in the frequency of complex partial seizures with secondary generalization. We observed an important change in seizure frequency from two seizures during the night to one seizure in ten days in the boy and from 6 daily seizures to one every four days with disappearance of daily seizures in the girl. The tolerability was good, and no adverse events were observed even if ESL was added to other antiepileptic drugs.
Conclusions: Despite the short-term and open nature of our study and the small number of patients, ESL has proven to be effective and tolerated in our cases of severe myoclonic epilepsy.

1. Introduction

Severe myoclonic epilepsy of infancy (SMEI), also known as Dravet syndrome, is an epileptic encephalopathy that presents during the first year of life and is one of the most severe types of infant epilepsy that is resistant to drugs [1,2].

Patients with Dravet syndrome display multiple seizure types including tonic–clonic, myoclonic, absence, and focal seizures. In addition to epilepsy, SMEI is associated with cognitive delays and behavioral disorders [2].

De novo SCN1A mutations are a major cause of SMEI [3]. In addition, mutations in *SCN1B*, *SCN2A*, and *GABRG2* also cause SMEI, and recently, a Dravet-like phenotype in which *PCDH19* and *CHD2* genes are involved was described [4,5].

Pharmacoresistance is one of the major problems in SMEI, and many antiepileptic drugs do not seem to be able to control all the different kinds of seizures, including generalized tonic–clonic seizures (GTCS) and myoclonic, absence, and focal seizures, which characterize this syndrome.

Eslicarbazepine acetate (ESL) is a relatively new antiepileptic drug which has been approved in 2009 by the European Medicines Agency and in 2013 by the US Food and Drugs Administration as adjunctive therapy in adults with partial onset seizures with and without secondary generalization. Eslicarbazepine acetate shows an important action on the blockade of voltage-gated sodium channel (VGSC). It has been recently reported that there are some differences between AEDs acting on VGSC that are also related to their different affinities for the channel based on the functional state of VGSC. In fact, three distinctive states have been shown for VGSC which include the resting state, the open state, and the inactivated state. The affinity of ESL for the inactivated

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state of these channels is similar to other AEDs (carbamazepine), while its affinity for the resting state is three times lower than the other drugs, thus preventing sustained repetitive neural firing but disturbing physiological mechanisms to a lesser extent. Another peculiarity of ESL has been reported by an experimental study which showed that this drug could reduce VGSC availability through enhancement of slow inactivation, as reported for lacosamide, while it seems not able to alter fast inactivation of VGSC, unlike carbamazepine (CBZ) and oxcarbazepine (OXC) [6]. In addition, the eslicarbazepine metabolite effectively inhibited high- and low-affinity CaV3.2 inward currents with greater affinity than CBZ [7].

We report a short-term open study about two patients affected by SMEI who both showed favorable response with regard to seizure frequency reduction when treated with ESL and good tolerability.

2. Methods

The first patient is a 17-year-old Italian boy with SMEI and a severe clinical outcome, in whom we identified a punctiform mutation (5053del AA fs1685X1691) in the α subunit of the neuronal sodium channel SCN1A gene. He started to have febrile and afebrile seizures at the age of 6 months. No drug treatment, including valproate, lamotrigine, carbamazepine, phenobarbital, vigabatrin, topiramate, clonazepam, ethosuximide, phenytoin, felbamate, nitrazepam, rufinamide, zonisamide, or lacosamide had proven effective (Table 1). The best results in the reduction of seizure frequency was obtained with a combination of phenobarbital, clonazepam, and zonisamide, showing a reduction of about 50% of partial complex seizures during sleep and 70% of daytime GTCS. During this time, the EEGs and clinical and epileptic characteristics of this patient showed typical features of SMEI such as slowing of background EEG activity with multifocal and diffuse discharges prevalent in the frontal regions, myoclonic seizures at the age of 2 years and 6 months, ataxia, and progressive intellectual disability.

At the age of 16 years and 6 months, we added ESL in combination with phenobarbital, clonazepam, and zonisamide at the initial dosage of 400 mg once daily and after two weeks at 800 mg/day. After just a few weeks from the start of therapy, we observed a complete response with disappearance of monthly GTCS and sleep frontal-partial complex seizures (with 3–4 occurrences per night previously observed). We did not observe adverse events during the treatment period of six months with a significant improvement in behavior, particularly oppositional defiant disorder and the maintenance of attention.

The second patient is a 21-year-old Italian girl. At the age of 11, we had identified a punctiform mutation (931G>T E311X) in the α subunit of the neuronal sodium channel SCN1A gene. The febrile and afebrile complex-partial seizures started at the age of 3 months.

Similar to the first patient, the drug treatment for this patient included acetazolamide and stiripentol that had not been proven effective (Table 1). In particular, at the age of 8, a combination of phenobarbital, clonazepam, and acetazolamide (250 mg/day) caused a decrease in seizure frequency of about 40%. The number of seizures was previously much higher and associated with several eyelid myoclonic seizures at a frequency of hundreds of occurrences daily and several massive myoclonias from the age of 3 years. Magnetic resonance imaging showed moderate brain atrophy, which did not progress during maturation, and brain interictal SPECT at the age of 2 showed hypoperfusion of the left frontal cortex. The EEG showed diffuse and multifocal paroxysmal activity that was more evident in the bioccipital regions. In the first year of life, the child showed unimpaired neuromotor development and hypotonia. She presented progressive intellectual disability, which became profound, as well as severe ataxia, making it impossible for her to walk. In addition, her speech was absent.

At the age of 10, a VNS device was implanted without any results.

At the age of 20, we added eslicarbazepine acetate to phenytoin, clonazepam, and valproate at the initial dosage of 400 mg once daily, which was increased after two weeks to 800 mg/day. We have also observed in this case good response with regard to seizure frequency reduction in just a few weeks after starting therapy. The girl does not present any daily seizures, just one seizure every four days currently.

3. Results

We observed a significant and fast effect using ESL as add-on therapy to other AEDs in both patients similar to what was reported in literature for adult patients with partial-onset seizures [8]. The peculiarity in our cases was the age when ESL therapy was started, 16 years and 6 months for the boy and 20 years for the girl, respectively, underlying the possibility of using ELS with good efficacy as an add-on therapy in young patients [9]. Of particular interest is ESL's efficacy in both patients with SMEI carrying SCN1A mutation because it is well known that seizure control is very difficult to achieve in this syndrome. The reason why ESL was effective in patients whose seizures are typically drug-resistant is not yet known; we could theorize that it could be due to the peculiar action of ESL on VGSC. Indeed, carbamazepine, which alters fast inactivation of VGSC, can worsen seizures and should not be used in

Table 1
Response and time of administration of AEDs in both patients.

AEDs	Time of administration		Response[a]	
	Patient 1: 17-year-old boy	Patient 2: 20-year-old girl	Patient 1: 17-year-old boy	Patient 2: 20-year-old girl
Valproate	2 years	18 years	1	2
Lamotrigine	6 months	5 months	1	1
Clonazepam	10 years	12 years	2	3
Carbamazepine	9 months	6 months	1	1
Phenobarbital	12 years	1 month	3	0
Vigabatrin	3 months	4 months	1	1
Topiramate	1 month	6 months	0	1
Ethosuximide	1 year	8 months	1	1
Phenytoin	2 months	10 years	1	3
Felbamate	1 month	3 months	1	1
Nitrazepam	3 months	2 months	1	1
Rufinamide	2 months	3 months	1	1
Zonisamide	4 years	4 months	2	1
Lacosamide	3 months	1 month	1	0
Acetazolamide	4 months	6 months	1	1
Stiripentol	4 months	4 months	1	1
VNS	–		–	1
Eslicarbazepine	6 months	6 months	4	4

[a] Number of daily seizures: 0 = increased daily seizures; 1 = unchanged seizures; 2 = reduction of seizures (less than 50% of frequency); 3 = reduction of seizures (less than 50–70% of frequency); 4 = reduction of seizures (more than 70% of frequency).

patients with SMEI [9]. It is interesting to note that in our cases, ESL has been used in combination with different AEDs, although benzodiazepine was the only AED common in both cases. Thus, it does not seem plausible that the effectiveness of ESL in patients with SMEI is attributable to the association between different drugs, but by analyzing the drugs in particular, we can observe their similar mechanisms, especially those on GABAergic system and voltage-gated sodium channel. Another peculiarity of our report is the effective dose of ESL, which was a low recommended dosage. Moreover, we observed a fast response to the initial dose of ESL [10].

4. Conclusions

Adjunctive eslicarbazepine led to seizure reduction in two patients with severe myoclonic epilepsy of infancy. Although this is a short-term open study, the results are promising but need confirmation.

Conflict of interest

The authors report no conflicts of interest.

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