Resolution of Seizures in A Child with Dravet Syndrome and Immunoglobulin G Subclasses Deficiency Treated with Valproic Acid, Intravenous Immunoglobulin, and Vagal Nerve Stimulator

Dana Hasbini [1*] • Ahmad Mansour [2]

[1] Rafic Hariri University Hospital, Beirut, Lebanon
[2] American University of Beirut, Beirut, Lebanon
ammansourmd@gmail.com

ABSTRACT: Severe myoclonic epilepsy in infants, also known as Dravet syndrome, is a rare refractory form of epilepsy and its control requires a combination of several antiepileptic drugs. We describe a child who had Dravet syndrome unresponsive to a combination of drugs. Work-up for repeated infections revealed immunoglobulin G subclasses deficiency. Administration of intravenous immunoglobulin in addition to valproic acid did not control epilepsy but followed by Vagal Nerve Stimulator, resolution of seizures was sustained.

To cite this article
[Hasbini, D., & Mansour, A. (2016). Resolution of seizures in a child with Dravet syndrome and immunoglobulin G Subclasses deficiency treated with valproic acid, intravenous immunoglobulin, and Vagal Nerve Stimulator. *The Journal of Middle East and North Africa Sciences*, 2(6), 27-29]. (P-ISSN 2412- 9763) - (e-ISSN 2412-8937). www.jomenas.org. **5**

1. Introduction:

Conventional antiepileptic drugs did not achieve seizure control in a child with severe myoclonic epilepsy; a combination of valproic acid, intravenous immunoglobulin for immunoglobulin G subclasses deficiency, and Vagal Nerve Stimulator achieved resolution of seizures. This novel combined approach (pharmacological, immunological and surgical) needs further evaluation in a subset of refractory severe myoclonic epilepsy.

2. Case Presentation:

This 8-year-old girl presented at the age of 4 years with a history of daily seizures since early infancy and recurrent episodes of prolonged febrile status epilepticus for more than 30 minutes necessitating multiple hospital admissions. Her seizures consisted of a combination of daily myoclonic fits, frequent focal, generalized tonic, and generalized tonic-clonic events upon febrile illness often ending up in prolonged status epilepticus. She was the product of a full-term pregnancy and a cesarean delivery with no perinatal complications.

She had borderline delayed neurodevelopmental milestones for age upon presentation and a difficult social interaction. Physical exam was unremarkable. Regular blood tests and thyroid functions test were non-revealing. Magnetic resonance imaging of the brain was normal. Multiple EEG recordings had frequent generalized spike waves and polyspike waves as well as multifocal abnormalities. A genetic blood test revealed a novel mutation c.5195C>T/p. Pro 1732Leu of the SCN1 (alpha subunit of the Type I voltage-gated sodium channel) gene that was not present in her parent's blood. Multiple medications were initiated including phenobarbital, valproic acid, topiramate, levetiracetam, lamotrigine, clonazepam, and clobazam, either as monotherapy or in different combinations, to no avail. The drugs did achieve therapeutic blood levels. The parents followed a strict regimen of adherence to medications and medical visits. Unfortunately, stiripentol was not available in our country.

Her neurodevelopmental delay and behavioral problems became more prominent. She was placed in a special school to meet her educational needs.

As she was noted to have very frequent febrile illnesses with accompanying seizures), the immune deficiency was suspected. Work up for immune deficiency revealed low levels of IgG2 (0.822 g/l), IgG3 (0.17g/l) and borderline IgG4 (<0.0691g/l), with the normal reference values being (1.06-6.1g/l), (0.18-1.63g/l) and (0.04-2.30g/l) for each respectively. Total IgG, IgA, and IgM levels were all normal. Upon these findings, the patient was kept only on Valproic acid (40 mg/kg/day) and was given a course of 2g/kg IV IgG (Octagam 10%-Octapharma AG, Lachen, Switzerland) over 5 days repeatedly, every month, for a total course of 6 months. Towards the end of the immunoglobulin course, the seizures were still refractory.

The decision then was to insert a vagal nerve stimulator (VNS- CyberonicsR, Houston, Texas). She underwent a smooth and uneventful surgery and was started on a gradual escalating program till

reaching the following parameters: a pulse width of 250 microseconds, a frequency of 20 Hz, a time on for 30 sec, a time off for 5min and an amplitude of 1mA. At that time, more than 50% of seizures had resolved and the febrile events had decreased from monthly to every 4 months.

Currently, the patient is seizure-free for more than 2 years. She is still on Valproic acid and under the same VNS parameters except for a time off for 1.8 min and amplitude of 2 mA. EEG continues to show frequent generalized high voltage and multifocal discharges. Her behavior has improved markedly and she has now better cognitive and scholastic performance with improved social interaction.

3. Discussion:

Dravet syndrome is a severe form of epilepsy with a great majority having a mutation in SCN1A gene, which encodes a voltage-gated sodium channel (Kwong et al., 2012). SCN1A-related seizure disorders are inherited in an autosomal dominant manner. A proband with an SCN1A-related seizure disorder may have an inherited or de novo mutation. The natural history of SCN1A-related seizure disorders is strongly influenced by seizure phenotype ranging from simple febrile seizures to severe myoclonic epilepsy of infancy.

Seizures in Dravet syndrome respond poorly to commonly used anti-epilepsy drugs. Initial results of clinical trials with newer medications (topiramate, levetiracetam), or with ketogenic diet appear promising (Chiron & Dulac, 2011). So far the best clinical response appears to derive from a combination of valproic acid, clobazam, and stiripentol (Al-Baradie, 2013). With this triple combination, both the frequency and the duration of seizures were reduced together with a decrease in the number of episodes of status epilepticus (Thanh et al., 2002). Stiripentol displays anti-epileptic effect by its effect on an alpha-3 subunit of the GABA-A receptors (Brigo & Storti, 2014). Recent studies have confirmed its efficacy as an add-on medication in Dravet syndrome (Inoue et al., 2009).

Stiripentol was granted an Orphan Designation for the treatment of Dravet syndrome in the US in 2008; however, the drug is still not FDA approved and is not available in a large part of the world, including Lebanon. A systematic review showed only 2 randomized clinical trials evaluating the use of stiripentol (total of 64 children) with findings of the significantly higher proportion of participants having 50% or greater reduction in seizure frequency in the stiripentol group compared with placebo (Inoue et al., 2009). Our patient's seizures were pharmaco-resistant. Thus, a more aggressive intervention was needed to decrease the seizures and secondarily delay progressive cognitive and mental deterioration (Van Rijckevorsel, 2006).

Concomitant administration of VNS and immunoglobulins in our patient in addition to valproic acid mono pharmacotherapy resulted in resolution of seizures.

As recurrent acute illness seemed to be an important precipitating factor for the development of seizures and status epilepticus in our patient, the evaluation of underlying immunodeficiency was warranted. However, a clear relation between immunodeficiency and Dravet has not yet between established and the literature concerning the subject seems scarce (Plebani et al., 1987). Young patients with IgG subclasses deficiency tend to develop recurrent infections as was noted in our young girl (Plebani et al., 1987).

Therefore administering IV immunoglobulins becomes an integral part of antiepileptic treatment in subjects with immunodeficiency and epilepsy (Berger, 2008). Several reports have dealt with immunological abnormalities in epileptic patients, especially low levels of immunoglobulins (Villani & Avanzini, 2002; Quek et al., 2012; Engelen et al., 1994; Nieto et al., 2000; Geva-Dayan et al., 2012; Geng et al., 2011). At the same time, and interestingly enough, IV immunoglobulin therapy has shown to be beneficial for some patients with certain types of intractable epilepsy, whether as an immune modulator or as a direct neuromodulator as has been proved recently (Villani & Avanzini, 2002; Quek et al., 2012; Engelen et al., 1994; Nieto et al., 2000; Geva-Dayan et al., 2012; Geng et al., 2011). Thus, IV IgG has a dual beneficial therapeutic role: the first being for immunodeficiency diseases and the second for some types of intractable epilepsies.

On the other hand, the beneficial role of VNS in children with intractable epilepsy is well established (Elliott et al., 2011; Kuba et al., 2009; Cersósimo et al., 2011; Zamponi et al., 2011). Data regarding VNS in patients with Dravet syndrome is still scarce.18 Emerging laboratory evidence suggests that VNS, while restraining inflammatory cytokine production in the peripheral nervous system, also exerts a significant CNS neuroprotective function against ischemic stroke injury (Jiang) by inhibiting the apoptosis and oxidant stress responses associated with such injury (Jiang et al., 2015).

It is unclear which of the above treatment played the major role in decreasing the seizures in our patient or whether there was synergism between the 3 modalities. IV immunoglobulin therapy could have helped to attenuate the seizures severity by the time the effect of the VNS started to work. Whether

the beneficial effect of the immuno-modulatory drugs like IV immunoglobulin therapy continues to work, long after its administration course is finished, is unknown. Therefore, IV immunoglobulin could have still helped our patient long after 6 months of the administration. However, it was clear that after the gradual escalation of the VNS parameters the seizures started to decrease markedly.

Corresponding Author:
Ahmad Mansour, Clin Prof.
American University of Beirut, Beirut, Lebanon
E-mail: ammansourmd@gmail.com

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Received May 27, 2016; revised June 03, 2016; accepted June 03, 2016; published online June 11, 2016.