Precision Medicine: *SCN8A* Encephalopathy Treated with Sodium Channel Blockers

Rikke S. Møller^{1,2} · Katrine M. Johannesen^{1,2}

Published online: 9 November 2015

© The American Society for Experimental NeuroTherapeutics, Inc. 2015

SCN8A, encoding the voltage-gated sodium channel Na_v1.6, was first implicated in epileptic encephalopathy in 2012 [1]. Since then, approximately 100 cases have been identified. *SCN8A* encephalopathy is characterized by onset of drug-resistant seizures at a mean age of 5 months (range 1 day–18 months), mild-to-severe intellectual disability, and developmental delay [2]. Patients develop multiple seizure types, including generalized tonic–clonic seizures that are present in most patients; tonic, atonic, myoclonic, focal, and absence seizures and epileptic spasms have also been described. Electroencephalography at the time of seizure onset is normal in approximately 50 % of cases. However, in the following months, most individuals develop electroencephalographic abnormalities, often comprising moderate-to-severe background slowing with focal or multifocal epileptiform discharges [2]. Prior to seizure onset, development is normal for approximately half of patients, and after seizure onset developmental stagnation or regression often results in mild-to-severe intellectual disability. Movement disorders such as ataxia and choreoathetosis are common, and hypotonia, hypertonia, and/or dystonia are present in 50 % of cases [2]. Sudden unexpected death in epilepsy has been reported in approximately 10 % of cases [2, 3].

The published mutations are all missense except for one splice site mutation resulting in an in-frame deletion [2, 3].

Most mutations arise *de novo*. The majority of the functionally tested *SCN8A* mutations result in gain-of-function (GOF), causing the Na_v1.6 channel to be hyperactive, leading to increased neuronal firing [1, 4–6]. Thus, it appears that neuronal hyperexcitability caused by GOF mutations is the predominant mechanism underlying epilepsy in *SCN8A* encephalopathy. Seizures in patients with *SCN8A* mutations are often refractory to conventional antiepileptic treatment. However, in approximately half of patients, good responses to anticonvulsants that directly modulate sodium channel activity (sodium channel blockers) have been described, either as a reduction in seizures or even seizure-free periods [2–4, 7–9]. In particular, carbamazepine and the derivative oxcarbazepine have proven useful in many patients. Limited clinical evidence suggests that sodium channel blockers may be the best treatments for patients with *SCN8A* encephalopathy. Nevertheless, further observations and specific functional data are still needed before we are able to understand fully and predict the effectiveness of these drugs in patients with *SCN8A* mutations. The GOF *SCN8A* mutations are in contrast to *SCN1A* mutations, which primarily result in the loss-of-function of voltage-gated sodium channels; in patients with *SCN1A* mutations (e.g., Dravet syndrome), phenytoin and carbamazepine are generally ineffective in treating the seizures.

In the current issue of *Neurotherapeutics*, Boerma et al. [10] report on four severely affected patients with *SCN8A* encephalopathy successfully treated with high doses of phenytoin. Prior to treatment with phenytoin, each patient had tried 3–5 antiepileptic drugs without sufficient effect. Freedom from seizures was achieved in 3/4 patients, with relapse of seizures when trying to taper off phenytoin [10]. Thus, the study by Boerma et al. [10] provides evidence for a treatment option in these severely affected children. Phenytoin is a sodium channel blocker that binds to a receptor site in the pore of sodium channels, decreasing sodium influx and thereby decreasing the excitability of the neuron. Sodium channels exist

This comment refers to the article available at: <http://dx.doi.org/10.1007/s13311-015-0372-8>.

✉ Rikke S. Møller
rmo@filadelfia.dk

¹ The Danish Epilepsy Centre Filadelfia, Dianalund, Denmark

² Institute for Regional Health Research, University of Southern Denmark, Odense, Denmark

in 3 main conformations: the resting state, the open state, and the inactive state; phenytoin binds preferentially to the inactive form. Carbamazepine is thought to have a similar working mechanism. However, the affinity of carbamazepine for inactivated sodium channels is around 3 times lower than that of phenytoin [11]. Phenytoin, like all other antiepileptic drugs, has adverse effects, including gingival hyperplasia, skin disorders, cerebellar atrophy, ataxia, polyneuropathy, and impact on liver function. Boerma et al. [10] report that high levels of phenytoin were required before optimal treatment effect was achieved. High serum levels of phenytoin increase the risk of irreversible adverse effects such as cerebellar atrophy and ataxia, and considering this, one could argue that sodium channel blockers with less severe adverse effect profiles, for example carbamazepine or oxcarbazepine, should be first-line treatment options for these patients. High doses of phenytoin could be considered in patients who do not respond adequately to other sodium channel blockers. In this small study by Boerma et al. [10] both the physician and the parents of the affected children considered the beneficial effects of the treatment to outweigh the adverse effects. The authors describe the first study suggesting phenytoin as a treatment option in patients with *SCN8A* encephalopathy. Further investigations are needed to elucidate the response to phenytoin of patients with *SCN8A* mutations.

During the last decade, next-generation sequencing technologies such as targeted gene panels and whole-exome sequencing have led to an explosion of gene identifications in monogenic epilepsies. In the short term, these findings will help with genetic counseling by providing information on prognosis and recurrence risks for patients and by providing families with a definitive diagnosis. In the long term, these discoveries may allow us to develop more effective treatments that can be targeted to the individual patient based on his/her genetic profile instead of empiric trials of medications broadly indicated for epilepsy. Monogenic epilepsies offer an excellent opportunity to achieve targeted treatments, also referred to as precision medicine, mainly because of the ongoing explosion in gene discovery, the existence of good animal and in vitro models, in which targeted medications can be developed, and

the ability to assess the efficacy of experimental targeted treatments in small clinical trials. The paper by Boerma et al. [10] illustrates the potential for genetic diagnosis in epilepsy to lead to specific targeted treatments.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Veeramah KR, O'Brien JE, Meisler MH, et al. De novo pathogenic *SCN8A* mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. *Am J Hum Genet* 2012;90:502-510.
2. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of *SCN8A* encephalopathy. *Neurology* 2015;84:480-489.
3. Wagnon JL, Meisler MH. Recurrent and non-recurrent mutations of *SCN8A* in epileptic encephalopathy. *Front Neurol* 2015;6:104.
4. Blanchard MG, Willemsen MH, Walker JB, et al. De novo gain-of-function and loss-of-function mutations of *SCN8A* in patients with intellectual disabilities and epilepsy. *J Med Genet* 2015;52:330-337.
5. Estacion M, O'Brien JE, Conravey A, et al. A novel de novo mutation of *SCN8A* (Nav1.6) with enhanced channel activation in a child with epileptic encephalopathy. *Neurobiol Dis* 2014;69:117-123.
6. Takahashi S, Yamamoto S, Okayama A, et al. Electroclinical features of epileptic encephalopathy caused by *SCN8A* mutation. *Pediatr Int* 2015;57:758-762.
7. Kong W, Zhang Y, Gao Y, et al. *SCN8A* mutations in Chinese children with early onset epilepsy and intellectual disability. *Epilepsia* 2015;56:431-438.
8. Ohba C, Kato M, Takahashi S, et al. Early onset epileptic encephalopathy caused by de novo *SCN8A* mutations. *Epilepsia* 2014; 55: 994-1000.
9. Singh R, Jayapal S, Goyal S, et al. Early-onset movement disorder and epileptic encephalopathy due to de novo dominant *SCN8A* mutation. *Seizure* 2015;26:69-71.
10. Boerma RS, Braun KP, van de Broek MP, et al. Remarkable phenytoin sensitivity in 4 children with *SCN8A*-related epilepsy: a molecular neuropharmacological approach. *Neurotherapeutics* 2015.
11. Kuo CC, Chen RS, Lu L, et al. Carbamazepine inhibition of neuronal Na⁺ currents: quantitative distinction from phenytoin and possible therapeutic implications. *Mol Pharmacol* 1997; 51:1077-1083.