

Lacosamide for SCN2A-related intractable neonatal and infantile seizures

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ABSTRACT – Voltage-gated sodium channel alpha subunit 2 (SCN2A) gene mutations are associated with neonatal seizures and a wide range of epilepsy syndromes. Previous reports suggest that traditional sodium channel blockers (SCBs) such as phenytoin, carbamazepine, and lamotrigine have a beneficial effect on SCN2A-related neonatal seizures, as they counteract the gain-of-function effect of mutated Nav1.2 channels. Additionally, SCBs are beneficial against other sodium and potassium channel-related neonatal seizures. There are, however, few reports describing the effect of the new SCB lacosamide against neonatal and infantile epileptic seizures. We report herein two neonates with intractable neonatal seizures with SCN2A pathogenic missense variants. Both infants showed temporary seizure relief following IV administrations of phenytoin, but were resistant to a combination of antiepileptic drugs, while complete seizure control was achieved following lacosamide administration. We suggest that SCBs, e.g. phenytoin, should be introduced early for refractory neonatal seizures of non-lesional and presumably genetic origin. If any beneficial response to a SCB is noted, this should prompt an initiation of additional SCBs. New clinical trials will provide data on the efficacy and safety of the new SCB lacosamide for genetic neonatal seizures and perhaps neonatal seizures in general.

Key words: SCN2A, neonatal, infantile, intractable, seizure, sodium channel blocker, lacosamide

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Voltage-gated sodium channels (VGSCs) play a cardinal role in the generation and propagation of action potentials in neurons and in most electrically excitable cells.

They are composed of one alpha and two beta subunits. The voltage-gated sodium channel alpha subunit 2 gene (SCN2A) encodes Nav1.2 (Catterall, 2000).

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Pathogenic variants of *SCN2A* were initially associated with benign familial neonatal-infantile seizures (BFNIS) (Herlenius *et al.*, 2007). Subsequently, their phenotypic spectrum expanded to include early infantile epileptic encephalopathy (EIEE) and epilepsy with migrating focal seizures (EIMFS) (Nakamura *et al.*, 2012; Baasch *et al.*, 2014; Howell *et al.*, 2015; Wolff *et al.*, 2017). Finally, epilepsies beyond the neonatal period, such as late-onset epileptic encephalopathies and some non-syndromic severe epilepsies (Liao *et al.*, 2010; Baasch *et al.*, 2014; Howell *et al.*, 2015; Schwarz *et al.*, 2016; Dilena *et al.*, 2017; Wolff *et al.*, 2017), with intellectual disability with/without decline, and autism spectrum disorders, have been associated with *SCN2A* mutations (Liao *et al.*, 2010; Baasch *et al.*, 2014; Schwarz *et al.*, 2016). This phenotypic variability is not fully understood. It is presumably related to the influence of the various mutations along with other pharmacogenetic modifiers and epigenetic factors (Nakamura *et al.*, 2012; Howell *et al.*, 2015; Wolff *et al.*, 2017).

Recent studies have documented a beneficial effect of traditional antiepileptic drugs (AEDs) with sodium channel blocking (SCB) properties against *SCN2A*-related neonatal seizures, including phenytoin, carbamazepine, oxcarbazepine, lidocaine, and lamotrigine (Nakamura *et al.*, 2012; Howell *et al.*, 2015; Schwarz *et al.*, 2016; Dilena *et al.*, 2017; Wolff *et al.*, 2017). There are, however, few reports of lacosamide, a relatively new SCB, for neonatal and infantile epileptic seizures. We hereby present two cases of newborns with intractable neonatal seizures with *SCN2A* missense pathogenic variants. Both infants were initially refractory to a combination of several AEDs, but seizure control was achieved only after lacosamide initiation.

Case studies

Patient 1

A female infant was born spontaneously at term after an uncomplicated pregnancy and delivery. Amniotic fluid and chromosomal micro-array analysis were normal. Birth weight and head circumference were 2,865 g and 33.3 cm, respectively. Physical examination was normal. She was the fourth child to healthy unrelated parents of European and Persian descents. There was a history of febrile convulsions and cognitive delay in some distant relatives.

The patient was readmitted on the fifth day of life because of poor feeding, sleepiness, and multiple daily episodes of a sudden cry, followed by head and eye deviation to the right side, flexion of the right hand, and extension of the left hand. The episodes lasted up to 30 seconds and were accompanied by a decrease in oxygen saturation, tachycardia, and postictal lethargy. Soon after admission, seizures involving the contralateral side were noted.

Initial EEG recording showed a burst-suppression pattern, interictal multifocal epileptiform activity, and focal right or left hemisphere electrographic seizures. Cranial ultrasound showed a small right choroid plexus cyst and mild bilateral periventricular hyper-echogenicity. Brain MRI at the age of nine days was normal except for a small, 3-mm area of restricted diffusion in the left frontal area, possibly indicating a clinically insignificant ischaemic lesion.

Metabolic work-up was normal including blood amino acids, carnitine, acylcarnitines, and uric acid; urine organic acids; and cerebrospinal fluid for lactate, glycine and neurotransmitters. Further investigation including blood and CSF cultures, echocardiography, fundoscopic examination, and abdominal ultrasound were also normal. Repeated head ultrasound and a follow-up MRI scan were normal. Hypercoagulability panel was normal.

The infant was initially treated with phenobarbital and soon after with levetiracetam with partial seizure control. EEG background activity normalised after three days, but interictal and ictal focal epileptiform activity continued on a daily basis (*figure 1*). Additional medications, including phenytoin, topiramate, pyridoxine, pyridoxal phosphate, and folinic acid, were gradually added (*table 1*). It was noticed that IV administration of phenytoin achieved temporary relief, but suitable blood levels could not be obtained. Therefore, oxcarbamazepine was introduced with partial improvement. Long-term seizure control was finally achieved after adding lacosamide on the 35th day of life, followed by gradual withdrawal of topiramate and oxcarbamazepine.

The patient has been seizure-free on lacosamide treatment. EEG at the age of four months was normal. At eight months, she had a generalized seizure after lacosamide was abruptly discontinued, and treatment was reinitiated. On follow-up examinations, the infant showed delayed visual maturation, intermittent esotropia, and central hypotonia. At 15 months of age, she demonstrates global developmental delay with a developmental quotient of 55, and communication and feeding difficulties.

An early infantile epileptic encephalopathy trio panel (Courtagene, using Illumina next-generation genomic panel) revealed a *de novo* c.778C>T P<Ala263val missense pathogenic variant in the *SCN2A* gene, confirmed by Sanger analysis.

Patient 2

A male infant was born via Caesarean at 37 weeks of gestation due to maternal reasons. Pregnancy was uneventful, except for fetal macrocephaly. Amniotic fluid and chromosomal micro-array analysis were

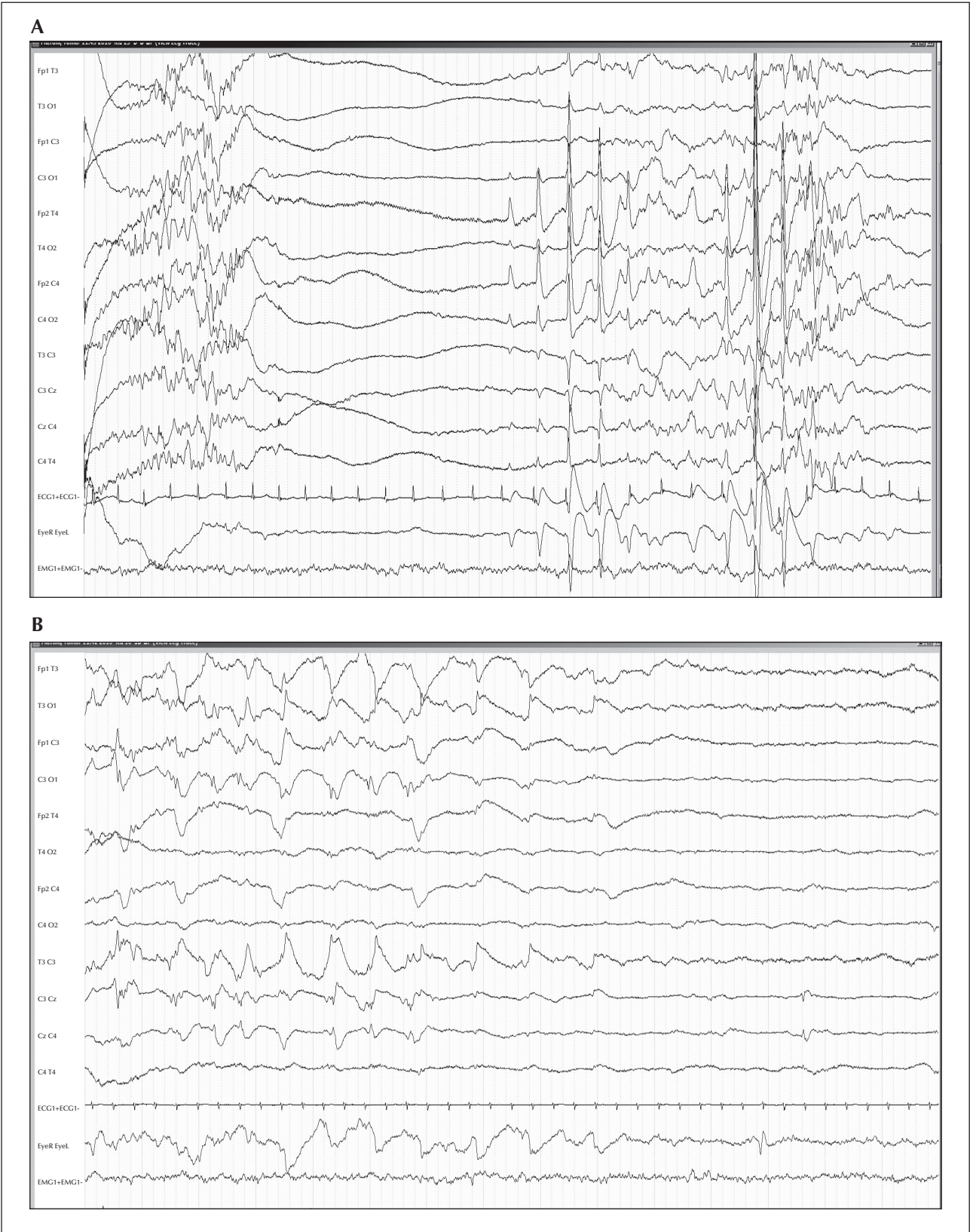
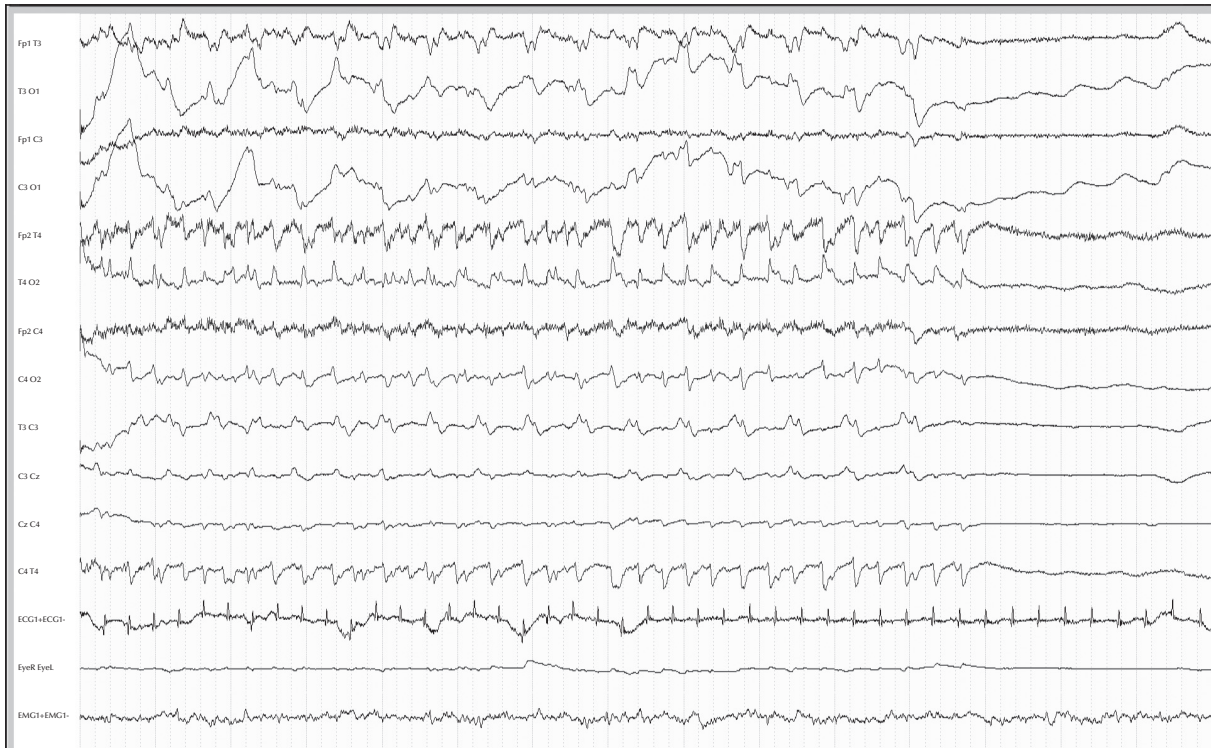


Figure 1. (A) Interictal EEG activity of Patient 1 showing burst suppression background intermixed with frontocentral epileptiform discharge (sixth day of life). (B) Slow central-temporal ictal discharge of Patient 1, arising from the left hemisphere, followed by postictal attenuation (tenth day of life) (Continued).

C



D

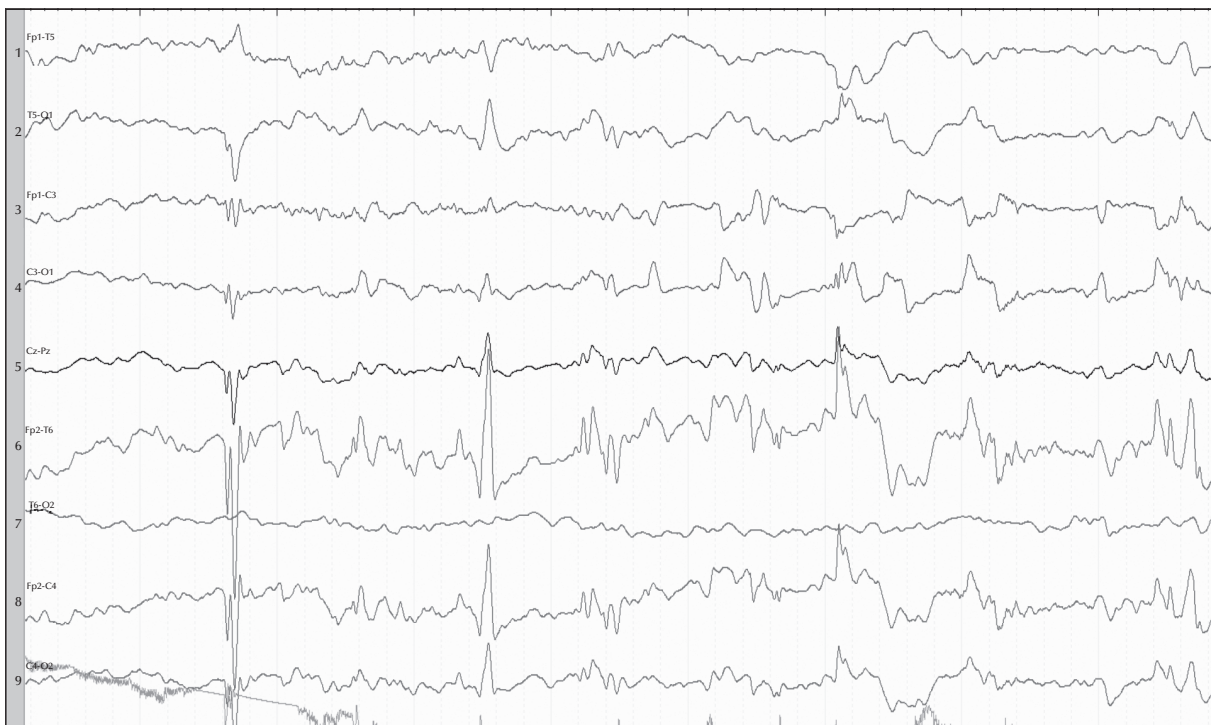


Figure 1. (C) A temporal-central epileptiform activity of Patient 1, arising from the right hemisphere, followed by postictal attenuation (tenth day of life). (D) Interictal epileptiform activity of Patient 2, arising from the right frontocentral, left central, and temporal regions (eighth day of life).

Table 1. Antiepileptic medications: dosing and duration of treatment.

Antiepileptic medications	Maximal dose (mg/kg/day)	Duration (days)	Maximal blood level (µg/ml)
Patient 1			
Phenobarbital	8	23	46
Levetiracetam	80	10	11
Phenytoin	6.6	10	6
Topiramate	16	26	
Pyridoxine	50	11	
Pyridoxal phosphate	33	19	
Folinic acid	7.5	19	
Oxcarbamazepine	40	21	
Lacosamide	20	900*	
Patient 2			
Phenobarbital	4	22	30
Phenytoin	6	45	8
Pyridoxine	33	1	
Pyridoxal phosphate	33	50	
Folinic acid	4.5	50	
Carbamazepine	15	14	3.7
Levetiracetam	50	22	
Valproic acid	20	3	53
Topiramate	15	26	
Vigabatrin	50	10	
Lacosamide	14	480	

*Ongoing treatment.

normal. Birth weight and head circumference were 3,300 g and 36 cm, respectively. Physical examination was normal. The patient was the third child of healthy unrelated parents of European descent. Distant relatives of his mother had mild intellectual disability.

Frequent seizures appeared on the second day of life. Episodes included a loud cry, flushing, increased extensor tone, and eye rolling, followed by apnea and oxygen desaturation and generalized hypotonia. Seizures lasted from a few seconds to three minutes. Neurological examination between episodes was normal.

Initial interictal EEG recordings were normal but epileptiform activity was captured on the amplitude-integrated EEG monitor. EEG recording at eight days showed multifocal epileptiform activity. Background EEG activity was normal on all EEG recordings (*figure 1*). Cranial ultrasound demonstrated bilateral lenticulostriate vasculopathy. MRI and MRS at the age of two days were normal.

Metabolic work-up, including blood amino acids, carnitine and acylcarnitines, urine organic acids, and cerebrospinal fluid glycine levels were normal except for a low HVA/5HIAA ratio and a low level of 3-O-methyl-dopa based on cerebrospinal neurotransmitter analysis. Echocardiography demonstrated a patent

foramen ovale, and blood and CSF cultures and fundoscopic examination were normal.

The infant was initially treated with phenobarbital and pyridoxine. After a short period of remission, seizures relapsed and additional medications were gradually added, including phenytoin, valproic acid, carbamazepine, levetiracetam, topiramate, vigabatrin, pyridoxal phosphate, and folinic acid (*table 1*). Seizures continued on a daily basis and it was noticed that IV administrations of phenytoin achieved temporary relief. Under combined treatment of phenytoin, topiramate, and vigabatrin, the frequency of seizures decreased, but seizure freedom was not achieved. After initiation of lacosamide at four months of age, full remission was achieved, followed by gradual withdrawal of topiramate and vigabatrin. At seven months, the patient had one generalized seizure after routine vaccination. On follow-up examination at 30 months, he was seizure-free with normal development and normal neurological examination.

Trio exome sequencing of the child and his parents (WES, ILLUMINA) demonstrated a novel, *de novo* missense pathogenic variant of the *SCN2A* gene, p.Met1545Ile- c.4635G>A, confirmed by Sanger sequencing. The variant was predicted to be pathogenic according to Mutationassessor, SNPS&Go, Mutation

Taster, and SNPs3D. The mutation has not been previously described according to aggregation databases of the general population (gnomAD and ExAC).

Discussion

We describe two neonates who presented with intractable neonatal seizures. Seizures were resistant to multiple AEDs. Both infants showed temporary seizure relief following IV administrations of phenytoin (a clue regarding a possible sodium or potassium channel epilepsy), while complete seizure control was achieved after adding lacosamide to a combination of AEDs. Genetic evaluation in both cases revealed *de novo* missense pathogenic variants of the *SCN2A* gene. The clinical presentations of both cases varied. Patient 1 (p.Ala263Val variant) presented with EIMFS. This pathogenic variant has been previously linked to self-limited neonatal/infantile epilepsy and later-onset episodic ataxia (Liao *et al.*, 2010) as well as EIEE (Ohtahara syndrome) (Touma *et al.*, 2013). A non-classified syndrome (including spasms and tonic and generalized tonic-clonic seizures) (Wolff *et al.*, 2017) was also reported. Patient 2 (p.Met1545Ile variant) presented with self-limited neonatal/infantile epilepsy (formerly called BFNIS). This pathogenic missense variant has not previously been reported.

Efficacy of traditional SCBs in *SCN2A*-related seizures has been explained by counteracting the gain-of-function effect of mutated Nav1.2 channels (Schwarz *et al.*, 2016). Only one prior study reported a beneficial effect of lacosamide treatment for *SCN2A*-related neonatal epileptic encephalopathies; of five infants, only one achieved seizure freedom, two had seizure reduction, and two showed no response (Wolff *et al.*, 2017). One can therefore assume that different mutations and heterogeneity of Nav1.2 channels make the response rate to lacosamide or other SCBs hard to predict (Catterall, 2000; Wolff *et al.*, 2017). In contrast to Patient 1, in two previous reports (Touma *et al.*, 2013; Wolff *et al.*, 2017) of patients with neonatal epileptic encephalopathies carrying the p.Ala263Val variant (Touma *et al.*, 2013; Wolff *et al.*, 2017), seizures were resistant to phenytoin. Lamotrigine, in combination with additional AEDs, resulted in a partial response (Wolff *et al.*, 2017) or complete resolution of seizures (Touma *et al.*, 2013). In both cases, lacosamide was not administered and therefore we cannot draw any conclusion regarding genotype and response rate to SCBs.

Paediatric neurologists and neonatologists often debate therapeutic options for refractory neonatal seizures and use a “trial and error” therapeutic strategy (Bassan *et al.*, 2008). In the current era of novel genetic analysis, the therapeutic approach to refractory neonatal seizures is becoming more targeted and

selective. Our study emphasizes the importance of very early genetic testing that may reveal the aetiology of refractory neonatal seizures and further influence the therapeutic approach.

We also suggest that SCBs, e.g. phenytoin, should be introduced early for refractory neonatal seizures of non-lesional and presumably genetic origin. SCBs may be effective against *SCN2A*- or other sodium channel-related neonatal seizures, and importantly, against the more common refractory neonatal encephalopathies due to potassium channel mutations (Pisano *et al.*, 2015). Therefore, when treating refractory neonatal seizures, a beneficial response to a SCB may constitute a clinical clue that should prompt initiation of additional AEDs with SCB properties.

Seizures were partially responsive to oxcarbazepine (Patient 1) and carbamazepine (Patient 2), while addition of lacosamide was followed by complete seizure freedom. Unlike most SCBs that affect fast inactivation of VGSCs, lacosamide affects the slow inactivation of VGSCs (Rington *et al.*, 2008; Rogawski *et al.*, 2015). Furthermore, in contrast to traditional SCBs that affect sustained repetitive firing (SRF) on a time scale of hundreds of milliseconds, lacosamide terminates SRF on a time scale of seconds and enhances the maximal fraction of channels that are in the slow inactivated state (Rogawski *et al.*, 2015). These properties of lacosamide and/or its additive response with other traditional SCBs may explain its favourable effect.

Lacosamide has an oral and intravenous formulation and therefore may be suitable for neonatal ICU use, perhaps for neonatal seizures in general. However, before adding lacosamide to the arsenal of SCBs currently used in neonatology, judicious use is necessary since the safety and pharmacological profile of lacosamide in neonates and infants is still unknown (Gavatha *et al.*, 2011; Heyman *et al.*, 2012). □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to declare.

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TEST YOURSELF



- (1) Which group of antiepileptic medication should be introduced early for refractory neonatal seizures of non-lesional and presumably genetic origin?
- (2) What is the mechanism of action of phenytoin in SCN2A-related seizures?
- (3) What is the difference between the mechanism of lacosamide and traditional sodium channel blockers?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".