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Abstract:
The Thr226Met pathologic variant of the SCN1A gene has been associated with the clinical development of an early infantile developmental and epileptic encephalopathy (EIDEE) different from Dravet Syndrome. The electrophysiological mechanisms of the mutated channel lead to a paradoxical gain and loss of function. The use of sodium channel blockers (SCB) that counteract this gain of function has been described in previous studies and they can be safely administered to patients carrying mutations in other sodium-channel subtypes without causing a worsening of seizures. We report the use of SCB in a child harbouring the Thr226Met pathologic variant of SCN1A with early onset pharmaco-resistant migrating seizures, as well as developmental delay. Lacosamide led to a dramatic reduction in seizure frequency, however, only a mild improvement in the epileptic activity depicted by Electroencephalography (EEG) was achieved. The introduction of Carbamazepine as an add on therapy lead to a notable reduction in epileptic activity via EEG and to an improvement in sensorimotor development. Despite the overall clinical improvement, the patient developed febrile seizures and a non-epileptic jerking of the right hand. In this case of EIDEE with the Thr226Met variant we demonstrate a beneficial pharmacological intervention of SCB in contrast to findings described in current literature. Our report encourages the cautious use of SCB at early stages of the disease in patients carrying this pathologic variant.

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Use of sodium channel blockers in the Thr226Met pathologic variant of SCN1A: A Case report

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Abstract

The Thr226Met pathologic variant of the SCN1A gene has been associated with the clinical development of an early infantile developmental and epileptic encephalopathy (EIDEE) different from Dravet Syndrome. The electrophysiological mechanisms of the mutated channel lead to a paradoxical gain and loss of function. The use of sodium channel blockers (SCB) that counteract
this gain of function has been described in previous studies and they can be safely administered to patients carrying mutations in other sodium-channel subtypes without causing a worsening of seizures. We report the use of SCB in a child harbouring the Thr226Met pathologic variant of SCN1A with early onset pharmaco-resistant migrating seizures, as well as developmental delay. Lacosamide led to a dramatic reduction in seizure frequency, however, only a mild improvement in the epileptic activity depicted by Electroencephalography (EEG) was achieved. The introduction of Carbamazepine as an add on therapy lead to a notable reduction in epileptic activity via EEG and to an improvement in sensorimotor development. Despite the overall clinical improvement, the patient developed febrile seizures and a non-epileptic jerking of the right hand. In this case of EIDEE with the Thr226Met variant we demonstrate a beneficial pharmacological intervention of SCB in contrast to findings described in current literature. Our report encourages the cautious use of SCB at early stages of the disease in patients carrying this pathologic variant.

**Key words:**

SCN1A  
Thr226Met  
Early infantile developmental and epileptic encephalopathy  
Sodium channel blocker  
Gain and loss of function  
Voltage gated sodium channel

**Abbreviations:**

CBZ  Carbamazepine  
DS  Dravet Syndrome  
EEG  Electroencephalography
Introduction

SCN1A variants associated with a loss of function in voltage-gated sodium channel (VGSC) NaV1.1 have been widely described and are correlated with a spectrum of epilepsy syndromes extending from the self-limited generalized epilepsy with febrile seizures plus (GEFS+) to Dravet Syndrome (DS) \(^1\)\(^-\)\(^3\). Impaired or mutated NaV1.1 channels, mainly expressed in axons and somata of parvalbumin-positive interneurons (PV), induce excitatory activity. Lower levels of functional NaV1.1 impair the local inhibitory circuits and networks driven by these interneurons\(^4\). Truncating SCN1A mutations cause premature truncation of the sodium channel protein leading to haploinsufficiency. Missense variants that cause mutations in the pore region are associated with loss of function similar to the result of haploinsufficiency. However, missense mutations located in the voltage sensor region results in gain- and loss-of-function of the channel (GOF and LOF respectively) \(^2\).

Recently, a Thr226Met missense mutation in the SCN1A gene was described and associated to a paradoxical GOF and LOF in sodium channel function, which correlates clinically with a more severe early infantile developmental and epileptic encephalopathy (EIDEE) \(^1\)\(^-\)\(^6\). The
electrophysiological mechanisms derived from this variant are multifactorial: the GOF is driven by a hyperpolarizing shift in voltage dependence of activation, which leads to enhanced action potential firing. Whereas the LOF is driven by an early excitation that leads to early depolarization block resulting in loss of excitability. Clinically this correlates with multifocal epileptic discharges driven by depolarization blocks.

The electrophysiological characteristics of this SCN1A variant has led to investigate the possible benefits of sodium channel blockers (SCB) as maintaining therapy, since these could reduce the availability of channels and lessen the sensitivity to depolarization block, counteracting the GOF properties. Nevertheless, a potential aggravation of seizures introducing SCB in patients with LOF-mutations have been previously reported. Brunklaus et al. 2022 described a cohort of GOF SCN1A-patients that showed a seizure reduction after administering SCB, however patients with the p.Thr226Met variant were refractory to SCB use.

Case report

A 12-week-old girl was referred to our hospital with early onset migrating focal, tonic and clonic, afebrile seizures. The pregnancy, perinatal and familial medical histories were unremarkable. The developmental milestones up to that age were accordingly achieved.

Seizures began approximately at 9 weeks of age showing tonic flexion of one or both legs immediately after waking up followed by erratic myoclonic jerks of the arms and crying (up to 1.5 minutes). When the symptoms exacerbated and were identified as pathologic, the child was admitted to the clinic.

Neurometabolic and imaging evaluation were unremarkable. The first electroencephalography (EEG) performed at the age of 10 weeks did not show any epileptic activity. At the age of 12 weeks this patient was transferred to our clinic and parietal discharges with alternating side appeared in the EEG Figure 1. A medication with Levetiracetam 60 mg/kg/d was introduced.
Clinical stability was achieved for only one week followed by alternating clonic seizures involving hands, legs, facial musculature, rapid eye blinking and unilateral atonic posture. Levetiracetam (90 mg/kg/d), Pyridoxin (300mg/Kg/d), Pyridoxal 5'-phosphate (30mg/Kg/d), Folate (3mg/kg/d), and Sulthiame (17mg/Kg/d) were given without any improvement. Ketogenic diet (KET) and Phenobarbital (PB) showed a temporary effect on seizure frequency and alertness. At the age of 7 months, we introduced Clobazam (0.5mg/Kg/d) due to clinical and EEG worsening (Figure 2-A). Nevertheless, our patient was never free from alternating hemiclonic seizures and myoclonus of the right hand (3-6 episodes per day), the EEG showed a gaining proportion of high amplitude and hypersynchronous activity (Figure 2-B). When the results of multigene panel testing (next generation sequencing with Nextera DNA Flex Pre-Enrichment LibraryPrep) that confirmed a heterozygote pathogenic variant c.677C>T, p.(Thr226Met) in the SCN1A gene were available, we introduced a therapy with the SCB Lacosamide (LCM) 8 mg/kg/d (blood level: 5.39 mg/l; therapeutic level: 1-10 mg/l).

This led to a massive reduction in frequency and intensity of seizures up to complete seizure remission, the non-epileptic jerking of the right hand remained. The EEG showed only little improvement, therefore Carbamazepine (CBZ) up to 12.6 mg/kg/d was added at the age of 11 months (blood level: 9.3 mg/l; therapeutic level: 8-12 mg/l). The follow-up-EEG after two weeks showed a reduction of epileptic discharges (Figure 2-C) and an improvement in the sensorimotor development was observed. Since the introduction of SCB only 3 febrile seizures were seen (hemiclonic and generalized tonic-clonic), therefore, Valproate (35mg/kg/d) was introduced (blood level: 36mg/l; therapeutic level: 50-100mg/l).

At the age of 5 months a developmental retardation with generalized hypertonia was first noticeable and progressed until the 12th month of age. In the meantime, after the introduction of SCB the girl interacts actively, grasps objects but still shows a massive hypotonia (stable sitting remains difficult). At the age of 17 months the child remains free from seizures without any epileptic discharges or encephalopathic pattern in the EEG.
Discussion

This report describes the effective use of SCB in a child harboring the Thr226Met pathogenic variant of the SCN1A gene associated with a mixed GOF and LOF.

Saidler et al., 2017 speculated a possible channel GOF in the Thr226Met pathogenic variant as seen in other subtypes of the VGSC (e.g. SCN2A and SCN8A). Berecki et al. 2019 demonstrated a paradoxical GOF and LOF in VGSC using electrophysiological studies. A key factor responsible for this hyperexcitation is a missense mutation in a conserved threonine residue in the S4 segment of domain I which accounts for most of the gating charge.3,9

The use of SCB to reduce availability of channels and lessen the sensitivity to depolarization block has already been speculated and tested on patients by Brunklaus et al., 2022. That study evaluated different GOF SCN1A cohorts and reported a seizure reduction in the majority of patients except in the group carrying the p.Thr226Met variant (10 Patients). 2 of these patients belonged to their study group and the other 8 were a part of the cohort studied by Saidler et al., 2017. For one of these two patients, Brunklaus et al., 2022 did not report the use of any SCB (Patient 22). In the second reported patient (Patient 23) the use of oxcarbazepine and carbamazepine is described as having “no effect”. However, they reported no worsening under this treatment either. A direct clinical comparison of these two patients with our case cannot be achieved, given the lack of use of Lacosamide. Saidler et al., 2017 did not report the use of LCM in any of their patients either. Additionally, none of these studies report the age of introduction of SCB. Consequently, we speculate that the combination of drugs that selectively enhance slow and also fast inactivation of VGSC10 led to the described improvement in our case. Furthermore, early introduction of SCB might have an impact on the clinical improvement as well. This would be in accordance with Wang et al., 201111 who reported a peak distribution of Nav1.1 at 7-9 months of age, which then decreased and stabilized during childhood and adulthood. Therefore, an early introduction of SCB might be crucial in achieving effective treatment.
The antiepileptic mechanism of SCB such as CBZ relies on the enhanced fast inactivation of VGSC mediated by an intracellular peptide loop located between domains III and IV, whereas the one for LCM has been associated with enhanced slow inactivation and is thought to be involved with the rearrangement of the inner pore structure. The development of febrile seizures after the introduction of SCB is susceptible to speculations. Several studies have investigated the effect of high temperatures in the development of seizures in models of DS, which account for the LOF properties of the channel. It has been described that at 40°C the mutant DIII voltage-sensing domain is altered by a shift in hyperpolarization and slows the action of the intracellular peptide loop, leading to fast inactivation. Therefore, at higher temperatures, the fast inactivation properties of the channel are enhanced leading to LOF.

Volkers et al., 2013 also found that the stability of the inactivation gates of the Nav1.1 channels are highly temperature sensitive. At 40°C the DS mutated variant showed fever-induced gating defects in combination with biophysical ion channel alterations that also led to LOF.

Overall, we speculate that the late development of febrile seizures in our patient are due to the use of SCB that counteract the GOF properties of the mutated channel, leaving the LOF properties intact, which are highly susceptible to temperatures as described before. In other words, after the effective introduction of SCB the clinical features of our patient shifted to a more DS-like phenotype.

We speculate that the remaining myoclonic jerks of the arm in our patient might be associated with a beginning movement disorder in terms of tremor or hyperkinesis and not as a result of epileptic activity.

Further research to investigate the electrochemical properties of the Nav1.1 mutated channel and to understand the mechanisms of the already described development of motor disorders as well as the association with fever, are warranted. More standardized clinical studies with the use of SCB for this particular mutation may improve the clinical state and quality of life of children carrying the Thr226Met pathologic variant of SCN1A.
Conclusion

The Thr226Met pathologic variant of SCN1A has been associated with a paradoxical GOF and LOF in the Nav1.1 VGSC and with a more severe EIDEE. We report the implementation of SCB treatment in a patient harboring variant that led to a clinical improvement in terms of reduction in seizure frequency and sensorimotor development, as well as reduction of epileptic activity demonstrated by EEG. Further long-term observational and larger studies are required to understand the clinical and pharmaceutical dynamics of these drugs in this cohort of patients.

Conflicts of Interests

The authors declare that they have no conflicts of interests.

Bibliography


**Figure captions**

**Figure 1:** EEG-recording at the age of 13 weeks. SI 10-20 longitudinal montage, 7uV/m, HF 35 HZ, LF 0.1 second. First pathologic EEG showing multifocal sharp waves.

**Figure 2:** EEG-recordings SI 10-20 longitudinal montage, 7uV/m, HF 35 HZ, LF 0.1 second. A) EEG at the age of 7 months. Seizures present while recording, clinically child staring with open deviated eyes, arms in abduction, legs in flexion. Spikes in the posterior and central brain regions in both sides. B) EEG at the age of 9 months shows hypersynchronous activity with sharp waves and spikes bilateral with secondary generalization. C) EEG at the age of 11 months shows an improvement in the background activity as well as isolated sharp waves.