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CASE STUDY

Carbamazepine efficacy in a severe electro-clinical presentation of *SLC13A5*-epilepsy

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Abstract

Recessive mutations in the *SLC13A5* gene encoding the sodium-dependent citrate transporter are a recently identified cause of developmental and epileptic encephalopathy. Here, we describe a child harboring a novel homozygous loss-of-function mutation in the *SLC13A5* gene (c.1496C>T–p.Ser499Phe) and exhibiting an unusual extremely severe neonatal presentation with drug-resistant seizures and burst-suppression EEG pattern. Early carbamazepine use resulted in dramatic improvement both clinically and on EEG features. Follow-up from the neonatal period to the age of 4 years is documented. This case expands the electro-clinical phenotype associated with *SLC13A5*-related disease and confirms the efficacy and safety of carbamazepine in nonstructural early-onset epilepsies.

Introduction

Developmental and epileptic encephalopathies (DEEs) are a highly heterogeneous group of epileptic disorders with different etiology and various degrees and combination of early-onset refractory seizures, abnormal interictal EEG, and neurological impairment, usually leading to a poor prognosis.[1] Treatment is mainly symptomatic and there is growing evidence of sodium channel blockers efficacy in KCNQ2-encephalopathy[2] and few others gene-related DEEs.[3,4] Recessive mutations in the *SLC13A5* gene that codes for the Na^+/citrate transporter (NaCT) are a recently identified cause of a distinct neonatal-onset DEE.[5] NaCT is expressed in neurons, hepatocytes, testis, and tooth cells. The exact pathophysiology of brain disease and epileptogenesis is not fully understood. Moreover, relatively few children with *SLC13A5*-related disorder have been reported and the full extent of the clinical, neurological, and epileptic phenotype is only beginning to emerge.[6–8] Therefore, the optimal management of these patients is far to be known.

Our aim is to describe the neonatal presentation and evolution of a patient, harboring an unreported homozygous mutation in *SLC13A5* gene, which dramatically responded to oral carbamazepine, in order to expand the electro-clinical phenotype and provide therapeutic indications.

Case Study

We report the case of a female baby, born from consanguineous parents, after a full-term pregnancy and uneventful vaginal delivery. She was admitted to NICU at 10 h of life for a first self-limiting episode of focal clonic arm movements, without evidence of CNS infection or glycemic/electrolyte imbalance. Seizures relapsed shortly after, involving independently both sides of the body.

Physical examination revealed a lethargic and hypotonic newborn with poor contact and weak grasping. Neither dysmorphic features, nor skin and ocular lesions were present. She was unable to feed autonomously and she needed noninvasive respiratory support. On 2th day, seizures became progressively closer, evolving into status epilepticus (SE). Continuous video-EEG monitoring showed a completely disrupted background activity with absent sleep and wake cycles, replaced by a burst-suppression (B-S) pattern (Fig. 1A), unrelated to any drug modification. Bursts were occasionally associated with tonic spasms of the upper limbs. Frequent (>5/h) bilateral tonic and non-migrating multifocal seizures with polymorphic semiology (eyelid or limb clonic movements, dystonic asymmetric limb posturing, chewing, and paroxysmal apnea with perioral cyanosis and desaturation) were recorded (Fig. 1B). Phenobarbital was ineffective and a trial with pyridoxine (100 mg intravenously) was performed, followed by oral administration of pyridoxal-5′-phosphate (10 mg/kg t.i.d) and folinic acid (2 mg/kg b.i.d), but no clinical or EEG modifications were observed. On day 4, phenobarbital was replaced by carbamazepine (starting at 2 mg/kg t.i.d. with daily increase of 2 mg/kg/dose until 8 mg/kg t.i.d), the only sodium channel blocker agent available as oral suspension formulation in our country at that time. In few days, we could observe a dramatic reduction in seizure frequency, associated with a significant clinical improvement. Indeed, from day 7, the infant was seizure-free and we were able to wean-off the respiratory support and the assisted nutrition by nasogastric tube. Although axial hypotonia persisted, she was globally more dynamic and interactive. Long-term video-EEG monitoring showed resolution of the B-S pattern replaced by a continuous EEG background and complete seizure suppression despite the persistence of occasional interictal abnormalities (Fig. 1C). An exhaustive diagnostic work-up, including brain MRI and a large panel of metabolic analyses, was unrevealing. Exome sequencing found a new variant in the *SLC13A5* gene (c.1496C>T–p.Ser499Phe). The infant harbored two copies of the altered gene, each one transmitted by a heterozygous unaffected parent. To establish the pathogenic role of this genetic variant and its consequences on citrate transport, we performed a functional study. As expected, the missense variant resulted in a loss-of-function mutation with no residual activity of the mutated NaCT (Fig. 2). After 6 months of seizure-freedom, febrile and nonfebrile focal clonic seizures relapsed, recurring with an average frequency of once per month. The child experienced three febrile convulsive SE while taking carbamazepine at the dose of 15 mg/kg/day. These episodes of prolonged seizures ceased all with the intravenous administration of 1–2 doses of diazepam (0.25 mg/kg/dose), except for one requiring a second line treatment with phenytoin (15 mg/kg IV) to manage breakthrough seizures after initial control. An example of ictal EEG is showed (Fig. 1D). Despite seizure recrudescence, the interictal EEG showed a well-structured background (posterior dominant 5 Hz activity on eye closure and symmetric sleep spindles) with infrequent multifocal spikes. After the increase of carbamazepine dose to 30 mg/kg/day, SE did not recur with a follow-up of 3 years. Only sporadic (less than five per year) and short-lasting focal seizures are still present and treatment tolerance is excellent. The child is now 4 years old and she presents with moderate global developmental delay. She is able to walk with an assistive device. Expressive language is poor while social skills are relatively preserved. Neurological examination reveals truncal hypotonia with increased peripheral tone and choreoathetoid movements. A growth retardation and a delayed tooth eruption are present.

Discussion

Our case-report gives detailed information about clinical and EEG aspects from neonatal period to infancy and early childhood in a proband harboring a novel autosomal recessive mutation in *SLC13A5* gene. Neonatal SE is frequently reported in *SLC13A5*-related epilepsy with a percentage as high as 57% of all published patients and clonic and tonic seizures are the main type.[8] Nevertheless, EEG background is relatively preserved in most patients with mild diffuse slowing described in a minority. Therefore, B-S EEG pattern seems to be an extremely unusual finding and it has been reported for only another patient who successively displayed profound developmental delay and refractory epilepsy with some improvement on stiripentol.[9] Our case confirms a wide electro-clinical spectrum of this rare epileptic disorder, including a severe neonatal presentation with motor and nonmotor focal seizures evolving into SE, encephalopathy and a highly disrupted EEG background, such as B-S pattern. In addition, we could record bursts-related tonic spasms that grouped in clusters and often preceded bilateral tonic seizures onset. Brief paroxysmal events such as (tonic) spasms and epileptic or non-epileptic myoclonus are described in association with others DEEs, with or without B-S pattern, suggesting their potential role as a marker of global cerebral dysfunction.[10]

Retrospective studies with the aim to define the most effective anti-seizure medications (ASMs) in *SLC13A5* epilepsy indicate that GABA-ergic drugs and sodium channel blockers provide the best results during the follow-up period.[7,8] Information about treatment efficacy in the neonatal period (the so-called "stormy phase") is scarce and carbamazepine was not considered in the NICU

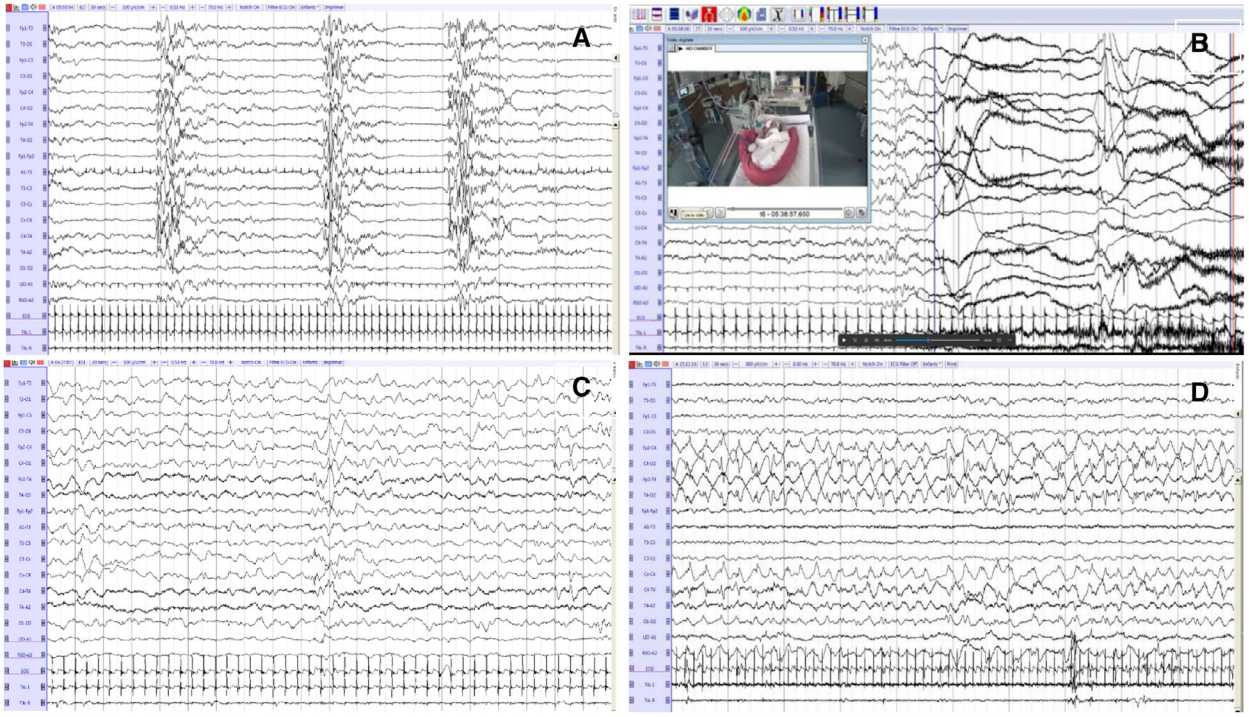

Figure 1. (A–D) EEG samples. Long-term EEG monitoring at 48 h of life showing a severe background with a pattern of burst-suppression, unrelated to drug infusion. Synchronous bursts (0.5–1-sec duration) of high amplitude polymorphic sharps and spike-waves alternated with low amplitude intervals that vary from 2 to 10 sec. The pattern persists in all stages of wakefulness and sleep. Time constant: 30 sec. Amplitude: 100 μV/cm. High band filter: 0.53 Hz. Low band filter: 70 Hz (A). Abundant ictal activity consisted of bursts-related tonic spasms, focal clonic and bilateral tonic seizures accompanied by upper limbs elevation and apnea. One example of bilateral tonic seizure is shown: note the flattening of electrical activity at seizure onset (blue line) and the saturation of EMG signal with the presence of muscular artifact on EEG due to the muscle stiffening. Time constant: 20 sec. Amplitude: 100 μV/cm. High band filter: 0.53 Hz. Low band filter: 70 Hz (B). Long-term EEG monitoring at day 7 of life (72–96 h after CBZ introduction) shows resolution of B-S pattern, replaced by a continuous electrical activity with identifiable awake and sleep states. Interictal multifocal sharps and spikes are occasionally observed. No seizure is recorded during 24 h-long monitoring. Time constant: 20 sec. Amplitude: 100 μV/cm. High band filter: 0.53 Hz. Low band filter: 70 Hz (C). After 6 months of seizure freedom, the child relapsed with prolonged focal seizures, and frequently triggered by fever. No other seizure type was present. Interictal EEG displayed a well-structured background. One example of ictal EEG at 13 months of age is shown: note the presence of high-amplitude rhythmic spikes on the right posterior quadrant diffusing to the right hemisphere, associated with staring, nystagmus, and eye deviation on the left side. Time constant: 30 sec. Amplitude: 300 μV/cm. High band filter: 0.3 Hz. Low band filter: 70 Hz (D).

therapeutic armamentarium until a few years ago. Our patient was treated with carbamazepine in a very early phase and we obtained an excellent and documented response, both clinically and on EEG background, despite initial severe presentation. Furthermore, we were able to avoid overtreatment with multiple ASMs and escalation with continuous infusion of sedative drugs that can potentially lead to additional neurocognitive sequelae in a developing brain. Whether the more favorable evolution observed in our case, compared to the patient reported by Alhakeem et al., is due to the major change in the current management of presumed genetic neonatal seizures with an advocated early carbamazepine trial, it is hard to prove. Interestingly, carbamazepine has for decades been excluded from the list of ASMs recommended for the treatment of early-onset epileptic encephalopathies. This is probably by analogy with West syndrome in which clinical and EEG aggravation or precipitation from focal epilepsy have been suggested with carbamazepine use.[11] Moreover, in our patient, a major issue could have been the presence of burst-related tonic spasms that could prevent from carbamazepine use in the concern of an exacerbation of such phenomenon. Nonetheless, this was relatively infrequent if compared to the more prominent feature of recurrent tonic and clonic seizures. Prolonged carbamazepine administration was safe and did not worsen epilepsy in our patient. On the contrary, during a new active epileptic phase occurring in early infancy, we could reduce again seizure burden and halt SE recurrence with higher doses of carbamazepine, avoiding potential side effects related to polytherapy. Dosage adjustments were made according to clinical effects and drug plasma concentrations.

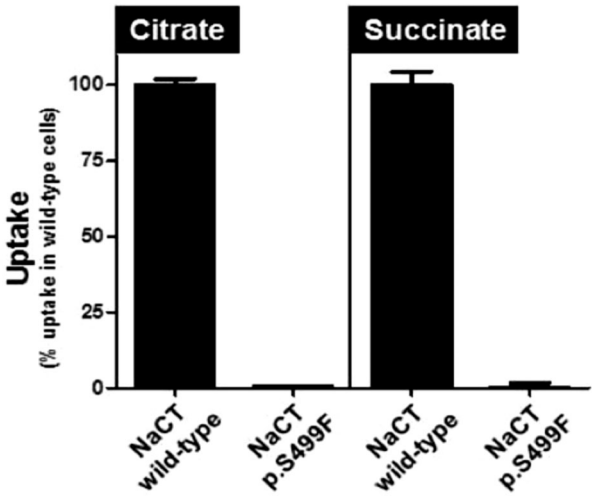

Figure 2. Functional study. After mutagenesis on the cDNA of SLC13A5 gene to obtain the c.1496C>T variant (verified by complete sequencing of the genetic transcript), uptake experiments with transiently transfected cells were performed, using the two prototypic NaCT substrates, i.e., citrate and succinate. As shown, the missense variant result in a loss-of-function mutation with no residual activity of the mutated NaCT. NaCT, Na^+/citrate transporter.

In our case-study, we report a new missense mutation in the *SLC13A5* gene whose pathogenicity has been assessed by a functional study, proving the complete loss-of-function of the mutated protein. In 2014, Thevenon et al. reported eight patients from three families (including one consanguineous family) harboring homozygous or compound heterozygous missense mutations in *SLC13A5* gene. In 2015 and 2016, Hardies et al. and Klotz et al., respectively reported eight and nine additional patients with different autosomal recessive mutations (missense, nonsense, and frameshift) in the *SLC13A5* gene. All patients developed ictal manifestations within the first week of life. Clinical evolution was marked by developmental delay (from mild to severe) and epilepsy with variable seizure burden. Patients had combination of ataxia, choreoathetosis, and spasticity; most of them displayed hypoplasia/hypodontia and/or failure to thrive.

In 2018, Selch et al. studied the effect of the mutations reported by Thevenon et al. in a cellular model, demonstrating that cells expressing mutant NaCT had a complete loss of citrate uptake.[12] Citrate represents a key molecule in different and interconnected cellular biochemical pathways; its depletion in the neurons determine the inability to meet energy demand and maintain cellular homeostasis, resulting in neuronal energy failure that is a known pathophysiological mechanism of neurological diseases. Attempts to restore cerebral energy metabolism using a ketogenic diet in patients with citrate transporter deficiency showed controversial results.[6,7] Moreover, extracellular citrate is a modulator of N-methyl-D-aspartate (NMDA) receptors activity by zinc (Zn^{2+}) binding. Zn^{2+} can selectively block central neuronal excitation mediated by NMDA receptors. Consequently, zinc chelation exerted by high plasmatic citrate concentrations may lead to enhanced NMDA activity that is a well-known pro-epileptic condition. Therefore, citrate supplementation does not seem to be a rational therapeutic option. For instance, our patient was administered oral citrate for a short period by her parents with no obvious improvement. On the other hand, the efficacy of sodium channel blockers on ictal manifestations in *SLC13A5*-epilepsy is unlikely to be related to citrate transport and metabolism and anti-seizures effects are mainly exerted by reduction of neuronal excitability. More than physiopathology, seizure semiology, namely the presence of tonic seizures, seem to be an indicator of sodium channel blockers responsiveness in genetic epilepsies.[13] Even in the era of genomic diagnostic approach, an accurate electro-clinical interpretation is still mandatory to define the main seizure type and address the adequate treatment.

In conclusion, our case expands the electro-clinical spectrum of a rare genetic condition and gives therapeutic indication for an early trial with sodium channel blockers. In addition, it represents a well-documented example of the new concept of DEE.[1] Even though we could promptly suppress recurrent seizures and "malignant" EEG pattern in the neonatal period, later the child developed neurodevelopmental disabilities, as the result of the underlying genetic disorder and despite a low seizure burden.

Author Contributions

R. S., A. A., J. K., C. V., and J. S. contributed to the conception of the study. R. S., A. A., and J. K. contributed to drafting the text and preparing the Figures. C. D. L. and A. V. contributed to the acquisition and analysis of data.

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None.

Conflict of Interest

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

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