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Case Report

Dravet syndrome in a 3-year-old pediatric patient: case report

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ABSTRACT

Dravet syndrome (DS) is a severe form of epilepsy that occurs during the first year of life. This is caused by mutations in the voltage-gated sodium channel and characterized by frequent, prolonged seizures often triggered by high body temperature (hyperthermia), developmental delay, ataxia, hypotonia, sleep disturbances which is treated by multiple antiepileptic drugs. In this case report, we will discuss a 3 years old male pediatric patient who presented with complaints of vomiting and lethargies followed by seizures and has been diagnosed with DS since the age of 6 months. He was given with multiple antiepileptic drugs and other drugs for his symptomatic management which resulted in a major drug interaction. From this case report, we will get a clear picture necessitating continuous monitoring in case of polypharmacy.

Keywords: DS, Pediatric, Electroencephalogram, Antiepileptic drugs, Drug interactions, Polypharmacy

INTRODUCTION

Charlotte Dravet first described DS in 1978 as severe myoclonic epilepsy of infancy (SMEI), and it was later renamed DS in 1989.[1] It is a rare early-onset genetic epilepsy syndrome characterized by intractable epilepsy and neurodevelopmental delays.[1,2] DS is a severe developmental and epileptic encephalopathy (DEE) caused by a mutation in the voltage-gated sodium channel.[3] This disorder is characterized by its onset before the age of 12 months, normal development prior to seizure onset, frequent and prolonged febrile seizures, refractory hemiclonic, myoclonic, and generalized tonic-clonic seizures, and later neurodevelopmental impairments such as cognitive deficits, intellectual disability, motor impairment such as ataxia, behavioral abnormalities, a distinctive crouching gait and other conditions like sleep problems and autonomic dysfunction. The majority of patients experience repeated episodes of status epilepticus (SE), which are frequently triggered by fever.[2,4,5]

The prevalence of DS ranges from 1 in 15,000 to 1 in 40,000. They also demonstrated that DS affects both genders equally. Typically, the first seizure episode occurs during the first year of life. A mutation in the SC1A gene is found in up to 85 percent of children affected with DS. With DS, mortality is high (range: 5.75-10%). The most common causes of death in DS patients are sudden unexpected death in epilepsy (SUDEP) and status epilepticus.[1,2,6]

DS is caused by de novo loss-of-function mutations (haploinsufficiency)in the SCN1A gene, located on chromosome 2q24 which codes for the voltage-gated sodium channel isoform NaV1.1 and was discovered in the year 2001. The voltage-gated sodium channel is made up of a primary α subunit (NaV1.1-NaV1.9, encoded by the genes SCN1A–SCN11A) and a secondaryβ subunit (a single transmembrane domain, 1-4, encoded by the genes SCN1B–SCN4B). Theα subunit is the target of various antiepileptic drugs because it forms the sodium channel pore. The β subunits interact with the α subunit and influence the localization of alpha subunits as well as channel properties. NaV1.1, which is encoded by SCN1A, a membrane protein of 2009 amino acids composed of four domains, each with six transmembrane segments. NaV1.1 is primarily expressed in cell bodies

and dendrites in the central nervous system, but it is also found in the axon initial segments of some interneurons, which play an important role in the synthesis and propagation of action potentials. SCN1A gene mutations cause a significant decrease in sodium current in GABAergic interneurons, influencing GABA inhibitory function and leading to neuronal hyperexcitability and seizures. Furthermore, decreased sodium current can affect Purkinje cells, resulting in motor dysfunction, as well as behavioral and cognitive problems.DS is not only found in SCN1A variants; mutations in other genes such as PCDH19, SCN2A, SCN8A, SCN1B, KCNA2, GABRA1, GABRB3, GABRG2, CHD2, CPLX1, HCN1A, and STXBP1 are uncommon but can result in DS-like phenotypes.[7,8]

In late childhood and adulthood, there is a natural tendency to reduce epileptic seizures. As a result, the clinical course can be divided into three phases. They are: Seizure onset (up to 12 months)-The first seizures associated with fever, and epileptic states appear, while psychomotor development is normal.

Worsening phase (between ages 1 and 5 years)-New types of seizures emerge, such as myoclonic, atypical absence, and focal seizures, and the psychomotor developmental delay becomes apparent around the second year of life.

Stabilization phase (before 10 years of age)-Motor disabilities such as crouching, choreoathetosis, pyramidal signs, and parkinsonian syndrome are observed.[9]

Pharmacological treatment includes the use of antiepileptic drugs. First-line agents include valproate and clobazam. Second-line agents include topiramate, bromide, stiripentol, highly purified cannabidiol, and fenfluramine. Other agents like levetiracetam, brivaracetam, perampanel, zonisamide and ethosuximide are also used. Non-pharmacological treatment includes a ketogenic diet and vagus nerve stimulation. Sodium channel blocking anticonvulsants such as carbamazepine, oxcarbazepine, lamotrigine, phenytoin and lamotrigine are contraindicated.[10,11]

We present a case report of a 3 years old male pediatric patient who was hospitalized for vomiting and lethargies followed by seizures and has been diagnosed with DS since the age of 6 months. He was on his regular medications.

CASE REPORT

A 3 years old male pediatric patient was admitted to a tertiary care hospital and presented with complaints of vomiting and lethargies followed by seizures. He was first taken to a nearby hospital and treated with IV antiepileptics and paracetamol, but the seizures persisted, so the patient was transferred to a nearby tertiary care hospital and treated with 2 mg of IV lorazepam and antiepileptics. The child was COVID RT-PCR positive and continued to have poor sensorium. He was performed with an MRI brain which showed T2w hypersensitivity with restricted diffusion involving almost the entire bilateral cerebral hemispheric cortex (sparing the anteroinferior temporal lobe)-? HIE and? post ictal edema, had further onset of seizure started on with IV levetiracetam and midazolam infusion. After 48 hours there was no further episode of seizure, so midazolam was stopped. He also had episodes of loose stools with no dehydration and was started with antibiotics. Ultrasound (USG) abdomen was done which showed acute pancreatitis. Valproate was withheld due to COVID, his sensorium improved and tolerated nasogastric (NG) feeds. Due to some personal reasons, he was discharged at the request and confirmed to be COVID negative before being admitted over here.

He is a K/C/O DS in the last 6 months of his age and had been on regular medication which includes 5 ml of syp. valproic acid BD, 5 mg of tab. clobazam half a tablet only at HS, 25 mg of tab. topiramate in the morning and 50 mg in the night, and syp. piracetam 5 ml BD was taken. His neonatal history reveals that he is a LSCS baby and weighed about 3 kg at birth and had delayed milestones.

During the time of admission, he had complaints of fever, vomiting, lethargies followed by seizures and loose stools. His MRI brain was done under sedation which revealed no definite abnormality. EEG was also performed and that showed delta activity slowing throughout the record. Relevant laboratory investigations were done and showed serum ammonia and creatinine phosphokinase (CPK) normal, started on antiepileptic dosage titrated which includes 7.5 mg of tab. clobazam BD and was converted to 2.5 mg in the morning and 10 mg in the night for 10 days, 30mgof tab. phenobarbitone BD given for 1day and stopped, 50 mg of tab. topiramate BD for 10 days, 20 mg of inj. Levetiracetam1dose was given through IV and was converted to syrup of 3.5ml BD for 9 days, 5 ml of syp. piracetam BD was given for 1 day and stopped. After 2 days of admission, he had 1 episode of tonic-clonic posturing and jerky movements of all 4 limbs lasting for 3 minutes, so he was given 20 mg of inj. Levetiracetam IV STAT. All the tablet form drugs were given via NG tube.

His symptomatic management includes 2.5 ml of syp. domperidone TDS for 5 days and was converted to 3 ml QID for the next two days for vomiting, 3.5 ml of syp. paracetamol TDS for 5 days and was changed to SOS for fever (when temperature increases above 100^{o}F), enterogermina liquid BD for 14 days, and IV fluids given for loose stools. He was started on NG feeds 80 ml/hour and stopped IV fluids. Suddenly, he was presented with complaints of irritability and decreased sleep and so was given 10 mcg of tab. clonidine HS for 9 days. As this state persisted, tab. clonidine dose was increased to 25

mcg HS and was also added with 3 mg of tab. melatonin HS for the next 16 days.

After 10 days of interval, he had recurrent episodes of dystonic movements and was started on 25 mg of tab. tetrabenazine ¼ of tablet BD for 4 days and was converted to ½ of the tablet for 13 days. His EEG was repeated which showed diffuse delta slowing noted and intermittent sharp wave discharges noted over the right temporal region. He was continued with the same antiepileptic drugs clobazam, topiramate, and levetiracetam and was also added with syp. sodium valproate of 2.5 ml BD for 17 days. He was also initiated on steroids 300 mg of methylprednisolone in 100 ml normal saline for 5 days, the child's parents were counseled about the need for IVIG; which was scheduled as per the protocol was given 10 grams for 2 days, followed by 0.5 mg of tab. risperidone half a tablet at night for 4 days and frequency was changed to BD for 8 days. After completion of IVIG he had fever spikes and was started with 1.125 mg of inj. piperacillin+tazobactam QID for four days. After completion of inj. methylprednisolone injection, he was started with oral steroids 5 ml of syp. prednisolone OD for 4 days and frequency was changed to BD for the next 6 days.

After 10 days, once again EEG was done and showed frequent right fronto temporal sharp wave discharges, and occasional left fronto temporal sharp wave discharges. Bilateral frontal sharp wave discharges right > left noted. He had complaints of vomiting and constipation given with 2 mg of syp. ondansetron for 3 days and 5mgofbisacodyl suppository given through rectally at night for one day and bowel opened. Due to the sudden onset of vomiting his USG abdomen was performed and showed normal that acute pancreatitis was resolved. Suddenly he developed startled myoclonus was noted along with myoclonic jerk the reason behind this is the interaction between tetrabenazine and risperidone and so risperidone was stopped. After the termination of risperidone, startled myoclonus along with myoclonic jerk did not occur.

No further episodes of seizure for more than 15 days and complaints of dystonic movements were reduced so the patient was discharged. His discharge medications include: Tablet melatonin 3 mg (0-0-1), tab. clonidine 25 mcg (0-0-1), tab. topiramate 50 mg (1-0-1), tab. clobazam (2.5 mg-0-10 mg), tab. Lorazepam 0.25 mg (0-0-1), syp. sodium valproate 5 ml (1-0-1) syp. levetiracetam 3.5 ml (1-0-1), tab. tetrabenazine 25 mcg (1/2-0-1/2), syp. prednisolone 5 ml (1-0-1), tab. junior lansoprazole 15 mg (1 [BF]-0-0), syp. sucralfate 5 ml (1-0-1) and syp. lactulose 10 ml (0-0-1).

DISCUSSION

A 3 years old male pediatric patient was hospitalized with complaints of vomiting and lethargies followed by his seizures. As he is a K/C/O DS in the last 6 months of his age and with the help of EEG findings, he was put on multiple anti-epileptic drugs clobazam, phenobarbitone, topiramate, levetiracetam, and piracetam. Suddenly, he presented with irritability and decreased sleep and was given clonidine and melatonin. Within a short interval, he developed dystonic movements and so was provided with tetrabenazine. Due to the persistence of his irritability, he has also added risperidone. As a result of polypharmacy, a drug-drug interaction was found between tetrabenazine and risperidone, so he developed myoclonic jerk and risperidone was also stopped because of this event.

Most patients require polypharmacy; practitioners must be aware of drug-drug interactions between new medicines, current anti-epileptic drugs, and other medications in order to manage comorbidities, and be familiar with therapeutic drug monitoring techniques and pharmaco-kinetic characteristics. Because polypharmacy is norm in DS, there are practical problems such as variations in anti-seizure medicines serum concentrations and the possibility of increased side effects, necessitating close monitoring and possibly dose modifications.[12,13]

The EEG findings in DS evolve with age and can be examined ictally and interictally. Most interictal EEG recordings are normal during the first year of life. Between the second and fifth years of life, the prevalence of epileptiform abnormalities rises. Generalized, focal, or multifocal anomalies such as multifocal spikes, waves, polyspike, and wave discharges, and a slowing of background activity become visible.[14,15]

The high frequency of poor sleep-in people with DS may be caused by a variety of circumstances. SCN1A mutations, which are present in more than 80% of cases, may be responsible for sleep disruption through the dysregulation of neural sleep networks. In children with DS, polypharmacy may potentially contribute to the high frequency of sleep disturbances.[16]

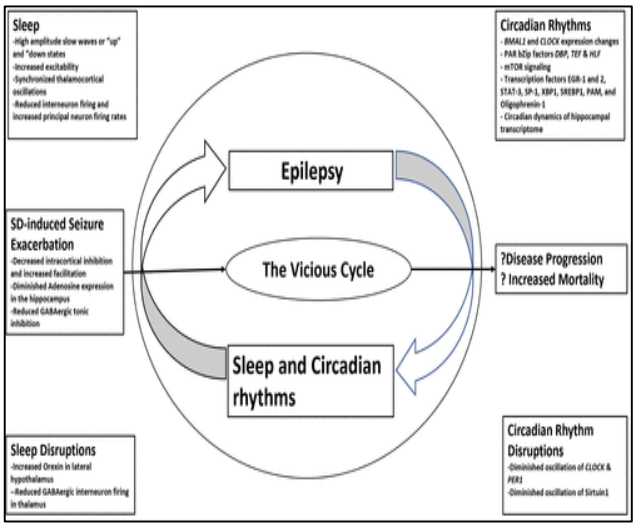

Figure 1: Relationship between sleep, circadian rhythm, and epilepsy.

Untangling a web: basic mechanisms of the complex interactions between sleep, circadian rhythms, and epilepsy[1]

The pineal gland releases the hormone melatonin in reaction to darkness and on a circadian schedule. In children with neurological and developmental issues, it is widely used as a hypnotic. Melatonin increases sleep latency and reduces alertness after falling asleep in children with seizures.[18]

CONCLUSION

Owing to the rarity of DS and the requirement of multiple drugs for the treatment leads to polypharmacy which may pave a way for drug interactions that could worsen the condition. Considering the age, and drugs used or administered there is a need for continuous monitoring inclusive of necessary investigations such as EEG. Thus, constant monitoring would help to avoid the progression of the disease.

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