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COMMENTARY

Two Perspectives on Dravet Syndrome: Viewpoints from the Clinician and the Caregiver

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ABSTRACT

Dravet syndrome (DS) is a severe genetic epilepsy characterized by early-life onset, seizures, and neurodevelopmental delays that have major impacts on affected children. DS is an incurable condition that requires a lifelong multidisciplinary approach involving both clinical and caregiver support. A better understanding of the multiple perspectives involved in the care of patients is necessary for supporting the diagnosis, management, and treatment of DS. Here we describe the personal experiences of a caregiver and a clinician facing the challenges of diagnosing and treating a patient throughout the three phases of DS. During the initial phase, the main goals include establishing an accurate diagnosis, coordination of care, and communication between clinicians and caregivers. After a diagnosis is established, frequent seizures and developmental delays are a major concern in the second phase, which is very taxing on children and their caregivers, so caregivers require support and resources to advocate for safe and effective care. Seizures may improve in the third phase, but developmental, communication, and behavioral symptoms persist as caregivers navigate the eventual transition from pediatric to adult care. Optimal care for patients is provided when clinicians are well educated on the syndrome and collaboration is established between members of the medical team and family.

Keywords: Dravet syndrome; Pediatrics; Caregiver; Clinician; Epilepsy

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Key Summary Points

Dravet syndrome (DS) is an incurable epilepsy syndrome that starts early in life and is characterized by seizures and neurodevelopmental delays

This article describes the perspective of a physician and a caregiver regarding diagnosis, treatment, and complications of a patient with DS

The perspective of the physician outlines the three phases of DS and highlights the important steps that physicians should take when treating DS patients

The caregiver's perspective describes the challenges that the patient faced due to a delayed diagnosis and their experiences with different treatments, and the impact this had on the family's quality of life

These perspectives suggest that the best patient care can be provided in an environment where the physician is well-educated about DS, the medical team collaborates effectively, and a mutual trust exists between the families and the neurologist

INTRODUCTION TO DRAVET SYNDROME: CLINICIAN'S VIEW

The constellation of early-life onset, medically difficult to control seizures (including both febrile and afebrile seizures), neurodevelopmental stagnation, and motor and communication difficulties, in the setting of mutations in the *SCN1A* gene is named after Dr Charlotte Dravet [1]. Throughout the 1970s, Dr. Dravet observed children with the above symptoms and became interested in understanding more about how these children were different from other children with epilepsy who have atypical neurological development. She has devoted years to studying and caring for them. Because of her invaluable hard work, thousands of neurologists around the world became educated on this disorder and have been able to provide better care to these patients. However, it was not until 2000 that the first gene mutations linked to the symptoms were identified [2].

Dravet syndrome (DS) is a type of epilepsy with a genetic basis that is uncommon (approximately 1:15,700 individuals in the United States, and 1:22,000–41,000 in Europe) [2, 3], tending to affect boys more often than girls [4], and often following a 3-phase course. It is a lifelong complex condition with many facets that require a careful and multidisciplinary approach.

Pharmacological treatment for DS is comprised of antiepileptic drugs, including Valproate, Clobazam, Stiripentol, Cannabidiol, Fenfluramine, and Topiramate, and other therapies including ketogenic diet and vagus nerve stimulator (VNS). Contraindicated drugs include sodium channel blockers such as Phenytoin, Carbamazepine, and Lamotrigine, and drugs acting on gamma-aminobutyric acid (GABA), such as Vigabatrin, Tiagabine, etc. Along with the pharmacological treatment, patients are also prescribed physiotherapy, speech therapy, and sleep medication to help with comorbidities [5].

Here, we present the perspective of a physician and a caregiver regarding the diagnosis, treatment, and complications of a patient with DS.

COMPLIANCE WITH ETHICS GUIDELINES

This article does not contain any new studies with human or animal subjects performed by any of the authors. Written informed consent to publish this report was obtained from the patient's legal guardian.

THE INITIAL PHASE: CLINICIAN'S VIEW

The initial phase in infants and toddlers is also known as a febrile stage [6, 7]. During this

period, children predominantly have seizures in the setting of fevers or minor illnesses [7]. One challenging aspect in this early phase is unintentional delay in proper diagnosis. This occurs because febrile seizures are quite common in the general pediatric population [8]. However, the type of febrile seizures that occur in children with DS tend to be quite long, often lasting more than 30 min (referred to as "status epilepticus") [6, 7]. Patients with DS who have had a high fever are prone to acute encephalopathy after status epilepticus [9, 10]. Sudden onset of central nervous system symptoms including convulsions followed by loss of consciousness are characteristics of acute encephalopathy, which is an important complication reported in children with DS [11]. The occurrence of a first long febrile seizure before the child's first birthday [3, 7, 12], as well as a focal presentation of symptoms (a seizure that affects either the left or the right side of the body) should elicit consideration of DS. Treatment of the seizures should be started during this phase, with daily medications to minimize seizure frequency, as well as rescue medication to prevent status epilepticus. Therapeutic decisions for seizure treatment should take into consideration the toxicity of certain antiepileptic drugs. Coincidentally, because the signature initial seizure occurs around the time when most children are immunized against many health-threatening infections, concerns about an association with vaccines as a cause of the disease often arises when counseling parents [13]. Many studies disprove this concern, and children with DS should be immunized to guard against acquiring preventable diseases that would place them at a greater risk of severe seizures.

As a physician, the main goals of this initial phase are:

- Early and accurate diagnosis based on genetic testing
- Treating seizures with daily medications while considering the toxicity of drugs
- Establishing trusted communication with parents to encompass the various aspects of care for these children
- Establishing seamless coordinated care with the child's pediatric physician
- Minimizing emergency department (ED) visits and safely keeping children out of hospital
- Educating parents on sleep time/nighttime safety matters, due to the risk of sudden unexplained death in epilepsy (SUDEP)

THE INITIAL PHASE, THE CAREGIVER'S VIEW: WILLEM'S STORY AND THE DELAY TO DIAGNOSIS

Willem's seizures started in 2001 the day after his 4-month measles, mumps, rubella, and pertussis vaccinations, so I initially was one of those parents who could not help but associate vaccinations with all the events that followed. When Willem was nearly 18 months old, he was diagnosed with autism spectrum disorder. He then started a long journey of speech, occupational and physical therapies, therapeutic nursery and kindergarten, and then inappropriate school after school in our efforts to help find some improvement for his cognitive delays, lack of speech, attention-deficit hyperactivity disorder, incontinence, and seizure disorder. We did not learn until he was 7 years old that his seizure disorder and cognitive and physical disabilities were caused by DS, and that the vaccinations triggered a fever and thereby "uncovered" DS, a genetic disease with which he was born.

THE SECOND PHASE: CLINICIAN'S VIEW

After the initial febrile phase, a second phase usually occurs between early childhood until late childhood/early puberty [6, 14]. The second phase is very taxing on children and their parents, because seizures of multiple different types occur at a very high frequency. Children in this phase of the illness often require multiple ED visits, resulting in hospitalizations, and the need to undergo several medication trials.

Often, a combination of medications is required to control the seizures. In this second phase, not only are seizures the predominant concern but developmental lags emerge. In addition, medications can also affect children's appetite, behavior, sleep patterns, and personality [15].

As a physician, it is important to do the following in the second phase:

- Ensure development is closely followed and children get early referral to multidisciplinary therapies
- Avoid "piling up" different anticonvulsants by tapering the unhelpful ones as a new medication is being added
- Perform necessary testing for proper surveillance of potential treatment side effects
- Always take time during the office visits to discuss "nonseizure" aspects of the child, such as appetite, sleep, social skills, behaviors
- Become an ally to parents to help them get support and resources so they can effectively and safely care for their child. This may mean advocating for the parents to get nursing services at home, one-on-one paraprofessional services for the child at school, limited commute to and from school, respite services for the family, and so on
- Educate the family on SUDEP

THE SECOND PHASE, THE CAREGIVER'S VIEW: LOST DEVELOPMENTAL TRACK

Because Willem was hyperactive and easily distractible, it was almost impossible for him to focus enough to learn. He went to school with children with autism because he had many features in common with them. He was cognitively delayed, nonverbal, and not toilet trained. He needed assistance with everything: eating, dressing, toileting, and all self-care. Initially, Willem exhibited some developmental gains, followed by phases of losing those gains; for example, after speaking about 15 words initially, his speech slowly disappeared. For the first 3 years, we hoped that his symptoms would resolve, and he would be back on some sort of developmental track. When that did not happen year after year, we became resigned to the heartbreak of a child who could not make progress. Over time, it became clear that any progress in typical learning would be very incremental. We hoped that, if we could control the generalized seizures, he would start to gain language and the ability to focus and learn, but we found our hopes of seizure control were fruitless and that the seizures did not stop. Unlike the autistic children with whom he went to school, Willem was always charming, happy, smiling, and very social. He easily made eye contact and loved the attention of enthusiastic teaching assistants.

SOCIAL ISOLATION AND ONGOING SEIZURES

During this time, I stopped working because it was very difficult to find caregivers who could handle a toddler's seizures potentially at any time, day or night. We had no nearby family who were willing or able to help, and were very much alone in coping with the complexity of this child. Our older child, a daughter, was 3 years old when Willem was born, and grew into a very independent, overachieving, self-sufficient girl who was mature beyond her age; typical of siblings of children with special needs.

Having a disabled child with such significant issues was isolating. We knew no other families who had children with DS. There was no way of getting to know the parents of other special needs children at his schools, and there was very little in the way of local support groups for children who were both medically and developmentally disabled. We were always sleep-deprived because many of Willem's seizures happened around 4:00–5:00 AM. He usually urinated during the seizure and needed to be changed during the night. The residual effect of his seizures and the resulting psychosis would leave Willem (and us) unable to go back to

sleep. The VNS device made a marked difference in controlling seizures. When he had a seizure while sleeping, we swiped a magnet over the battery in his chest and the additional charge from the VNS calmed the residual seizure activity. We were then all able to get some sleep.

INEFFECTIVE TREATMENTS

With the help of his pediatric neurologist, Willem went through one seizure medication after another, usually on a cocktail of three or four seizure medications at a time. We kept a detailed log of all his seizures, how long they lasted, when they happened, and what precipitated them. We found the doctors initially would tweak the medications, raising doses gradually, checking blood levels, until it was clear they were not effective, and then we would titrate him back off, sometimes after bad side effects and overdoses.

We tried numerous diets to control the seizure activity, but he was a difficult eater. We tried controlling the things that would trigger his seizures, regulating his sleep and his desire to be constantly active, in the hope that it might prevent seizures. We tried preventing him from overheating, knowing heat could trigger his seizures. Anxious to prevent him from any illness and fever that would trigger his seizures, we became germaphobes. We tried to control his environment, but it was impossible because he needed to go to school.

Prior to Willem having a precise diagnosis, we even tried brain surgery. Over the years, we had spent numerous weeks in the hospital with Willem while he had electroencephalograms to identify the location of his seizure focus. When he was 6 years old, we were advised to undergo a strip band study only to find that there was no focal location for his seizures. If we had known then that he had DS, we would have known he did not have a localized seizure focus and therefore surgery was not an option.

THE GIFT OF A DIAGNOSIS

When Willem was 7 years old, we finally learned he had DS. We found a new pediatric neurologist specializing in DS, who put him on Depakote, which finally stopped his daytime seizures. The seizures then dwindled to once a week, occurring about an hour after he fell asleep or an hour before he would awaken. We were able to take him off rescue medications and supplements.

After Willem's diagnosis, I discovered he was eligible for a home health aide paid for by applying for a Medicaid waiver. Now that we had a diagnosis, this was one of the most important steps we took for Willem's and our family's care. After considerable effort, we found a trained professional who came to our house to be with him after school until he fell asleep, and on weekends for 6 h a day. This allowed me to go back to work and meant we could spend more time together as a couple and a family, ultimately saving our well-being.

THE THIRD PHASE: CLINICIAN'S VIEW

The third phase of DS tends to occur well into adolescence [6, 14]. This phase is characterized by relative improvements in seizure frequency and intensity, but continuation of the developmental, communication, and behavioral symptoms. Gait difficulties are common, and a consultation with a pediatric orthopedist may be needed. Patients progressively develop crouch gait and skeletal malalignment in the second decade of life, thus compromising mobility and independence [16]. Further, the adult motor phenotype of patients with DS is characterized by anterocollis and parkinsonian gait [17, 18]. As patients grow older, they are often not sharing the bedroom with parents, so discussing nighttime safety is again of capital importance. There are a number of devices that can detect most seizure types and alert parents. Breathable pillows are also available. During

this phase, families often start researching suitable living programs for neuro-atypical young adults, and may also need to seek counsel about guardianship.

As a physician, it is important to do the following in the third phase:

- Help parents find a primary care physician with experience in the neuro-atypical population
- Continue to monitor for potential side effects
- Educate on continued SUDEP awareness

THE THIRD PHASE, CAREGIVER'S VIEW: OTHER COMPLICATIONS

Willem already had a long history of wheezing after getting a cold, but suddenly he began to get pneumonia more regularly. One day he would be at home sick with a fever, the next day he would be hospitalized and intubated for sepsis for 5 weeks, and we would be uncertain of whether he would survive. Taking shifts to be with Willem in the hospital became something we were good at, but this was the greatest challenge we had faced since we did not know if he would make it. After the hospitalization with sepsis, a new pulmonologist diagnosed him with bronchiectasis. We found that if we thickened his fluids and pureed his foods we could prevent the aspirations that were causing pneumonia to recur.

As Willem got older, it became apparent that his crouched gait was becoming severe. He became less stable and needed assistance to get around. He propelled himself by running forward, but his hips, knees, and feet were not developing normally. Orthopedists suggested braces and that there was little else to do. One orthopedist suggested surgically breaking his hips/knees and ankles and resetting them at his clinic, where we would have to live for 6 months. However, even with that extreme solution there was no guarantee there would be significant improvement to his gait, so we made the very difficult decision against this option.

We also tried to find a medication to help with Willem's attention-deficit hyperactivity disorder. If he could be less active and focus, we thought maybe he could learn. However, the medications we tried only made everything worse and appeared to make him psychotic; he did not sleep for a week, then we did not sleep for a week trying to titrate him back off medications. It was the final crisis that made us reevaluate our ability to care for him.

THE RESOLUTION

With many special needs children, there is a point when parents realize that they are not enough, and that their child needs the help that only a team can provide. At age 15, Willem had become so big, and his care so complex, that we realized his care was going to take more than what we, as a family, even with a home health aide, could provide. We found an amazing therapeutic residential program that was very well equipped to handle children with severe medical and developmental disorders. Its distance from our home meant we would spend a lot of time traveling to visit, but it also meant we were no longer in crisis as a family. However, even with a team of experienced professionals to care for him, we are still concerned about keeping him alive. The seizures are still a concern, but now the complication that keeps us up at night is how to better control and prevent the chronic aspiration pneumonias that put him in hospital on a regular basis, and are now the long-term threat to his life. We now have to consider a feeding tube to help prevent the aspirations.

CLOSING

According to Voltaire, "the art of medicine consists of amusing the patient while Nature cures the disease." DS is a perfect example of an exemption to his quote. Caring for children with this disorder is a marathon, not a sprint. Optimal care is best provided when clinicians are well educated on the syndrome, optimal collaboration is established between all members of the medical team, and an airtight

alliance of trust and compassionate care is present between the families and the neurologist.

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