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CASE REPORT

Dravet's Syndrome; A Catastrophic Epileptic Syndrome

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ABSTRACT

It was first described by Charlotte Dravet in 1978 and has been recognized as a syndrome by the International League Against Epilepsy since 1989. It starts in the first year of life frequently with febrile seizures (FS) in an, otherwise, normal infant. This is followed by refractory and mixed type of seizures. "Dravet's syndrome" (DS) previously named severe myoclonic epilepsy of infancy (SMEI), or epilepsy with polymorphic seizures. DS is caused by a mutation in the neuronal sodium channel gene, SCN1A , that is also mutated in generalized epilepsy with FS+ (GEFS+).

Key Words: DS (Dravet's Syndrome), neuronal sodium channel gene, SCN1A, Epileptic encephalopathy

INTRODUCTION

Dravet's Syndrome (DS) was first described in 1978 by Charlotte Dravet in Marseille, France and it was briefly reported in a French medical journal[1]. Soon afterward, it was recognized in Italy by Bernardo Dalla Bernardina and they together presented their first 42 cases diagnosed in Marseille, at the International Epilepsy Congress in Kyoto in 1981[2]. The seizures start in the first year of life, initially as febrile seizures (FS) in an, otherwise, normal infant. The FS are usually atypical. This is followed by refractory and mixed type of seizures.

It was first described by Charlotte Dravet in 1978. DS is recognized as an epileptic syndrome by the International League Against Epilepsy since 1989[3]. Initial symptoms typically include prolonged, febrile, clonic or unilateral convulsions, which often progresses to status epilepticus[4,5]. Later on, seizures occur without fever. Between the ages of 12 and 48 months, other seizure types emerge, commonly myoclonic, partial and atypical absence. Progressive slowing of psychomotor development, which may include regression of acquired skills, also becomes apparent during this time frame[4,5].

According to the ILAE, the DS is considered an "epileptic encephalopathy", defined as a disease in which epileptic activity leads to cerebral insult and cognitive dysfunction. It is not yet known whether the cognitive delay noted early in the disease is in fact an early stage of the disease. Clinical diagnosis can be genetically confirmed in about 80% of patients. Since first described, DS has been increasingly recognized worldwide; yet it remains a rare disorder with an incidence of probably less than 1 per 40,000. Its prevalence in children with seizure onset in the first year of life varies between 3 and 8%[6]. At the time of first febrile seizure the initial EEG is usually normal, and without any epileptic activity. Although photosensitivity / photconvulsive response can be seen early in the course of the disease. Photosensitivity is observed in about 42% of patients, though it is often transient[3]. In the second year of life, myoclonic seizures begin and EEG abnormalities are associated. Generalized spike-and-wave or polyspike-and-wave activity is seen during the seizures. Subsequently absence seizures develop and they are associated with 3Hz spike-wave discharges. The generalized discharges increase during drowsiness associated with focal and multifocal abnormalities. Seizures

get precipitated by eye closure in some. Over time some of the children show slowing in the EEG consisting of diffuse theta and less frequently delta activity. Later generalized spike-wave activity changes to spikes and spike-wave discharges localized centrally or at the vertex. Other neurologic signs, such as ataxia, may also appear. Dravet's syndrome is a rare disorder. Initial estimates from the 1990's place the incidence at one per 40,000 and one per 20,000, representing 3% to 5% of all severe epilepsies beginning in the first year of life[6].

The mortality rate is estimated at 16% and is usually attributed to accident, complications of a seizure, or sudden unexplained death in epilepsy (SUDEP) [7]. SCN1A is currently the most clinically relevant gene known to cause epilepsy[8].

Research continues to expand the phenotypic variability and it has been suggested that Dravet's syndrome is the severe form of a broader clinical spectrum. Mutations in SCN1A contribute to up to 80% of reported cases of Dravet's syndrome[8-10].

CASE REPORT

Three-years-old boy was referred to children hospital with uncontrolled seizures. He was born at term to a 24-year-old female after an uneventful pregnancy. His birth weight was 2.9 kg, and was discharged from hospital at the same time with the mother in healthy state. He was the third child of consanguineous Saudi couple. At the age of four and half months he developed high grade fever and parents noted jerking of one half of the body, which then spread to the whole body and lasted spontaneously after 5 minutes. Her elder sister was a known case of febrile seizures and developmentally she was normal.

He was admitted to local hospital and was empirically treated for meningitis for two weeks because parents did not consent for lumbar puncture. He was discharged after successful treatment with follow up in the neurology clinic. At the age of 6 months he was admitted again with febrile status epilepticus. At that time, CAT scan of the brain, EEG and lumbar puncture were performed, showed normal results. Later he had multiple admissions with febrile, a febrile seizures and couple of episodes of status epilepticus.

When he was referred to our hospital he was evaluated thoroughly and found to have global developmental delay. He had mixed types of seizures - generalized tonic clonic, absence and myoclonic jerks. He was treated with multiple anti-epileptic drugs, which include phenobarbitone, carbamazipine, clonazepam, clobazam and valproic acid but without much benefits. His developmental milestones were normal with ability of sitting at 6-7months of age and standing at 12 months of age but his speech was delayed from start and his social development was also delayed. In the second year of life, he developed daily myoclonic and hemiclonic seizures with steady cognitive decline. He was also noted to have some behavioral disturbance with hyperactivity. He has been followed in our neurology clinic for six months Levitracetam and Topiramate were tried but he failed to respond.

Routine blood, serum chemistry, ABGs, blood ammonia and serum lactate tests were within normal limits. His metabolic screening was also normal. MRI of the brain and magnetic resonance spectroscopy (MRS) were also unremarkable. Multiple EEG's were done and showed different epileptiform discharges and frequent photo-convulsive responses. EEG findings subsequently appeared to change progressively with appearance of generalized, focal and multifocal spikes and sharp waves. Background EEG activity varied between normal and slow.

In our neurology follow up most drugs had proven ineffective. On the basis of clinical course, uncontrolled mixed types of seizures and delayed and regression of developmental milestones Dravet's syndrome was suspected and he was referred to higher research center for further evaluation. He was investigated thoroughly there and genetic analysis was done for SCN1A mutation, which was found to be positive, confirmed the diagnosis of Dravet's syndrome.

DISCUSSION

It was first described by Charlotte Dravet in 1978 and has been recognized as a syndrome by the International League Against Epilepsy since 1989[2,3]. Dravet syndrome is considered to be one of the catastrophic pediatric epilepsy syndromes. Initial symptoms typically include prolonged,

febrile, clonic or unilateral convulsions, which may progress to frequent status epilepticus[3,4]. Later on, seizures occur without fever. Between the ages of 12 and 48 months, other seizure types emerge, commonly myoclonic, partial and atypical absence[5].

Dravet syndrome is characterized by febrile, afebrile, generalized or unilateral clonic or tonic-clonic seizures that appear in the first year of life in previously healthy infants. After the first year, the clinical features are accompanied by myoclonia, atypical absence and complex partial seizures. It is not classified as focal or generalized epilepsy by the ILAE, but rather as an epileptic syndrome[11]. All seizure types are resistant to antiepileptic drugs.

Simple partial seizures occur in approximately one third of the patients, partial seizures with secondary generalization in 20% and repeated episodes of status epilepticus in approximately 10%[12]. Our patient had repeated episodes of partial seizures, myoclonic jerks, and generalized tonic clonic occurred and multiple episodes of status epilepticus.

It is not classified as focal or generalized epilepsy by the ILAE, but rather as an epileptic syndrome[12]. The patients generally have frequent episodes of status epilepticus. The aforementioned seizure types and status epilepticus were seen in our patient. After the initial epileptic seizures, most of the patients had status epilepticus that was mainly associated with fever[2].

After the second year of life, in which seizures occur more frequently, developmental and cognitive regression with behavioral disorders and hyperactivity occurred in our case.

There are several reasons for seizures and developmental regression in infancy. Some of them were incorrectly identified as vaccine encephalopathies[13]. However, later studies did not support the link between permanent brain damage and vaccines[14]. On the other hand, similarities were observed between clinical progressions of SMEI and vaccine encephalopathy as more data was gained about special epilepsy syndromes like Dravet's syndrome. Berkovic *et al*. detected *SCN1A* gene mutations[15].

As the initial seizures are often associated with fever, distinction from benign febrile convulsions is important. In Dravet syndrome, the seizure type is frequently clonic or hemi-clonic rather than generalized tonic-clonic, the seizures are more prolonged and frequent, even when treated; and hyperthermia is a triggering factor even when temperature elevation is moderate.[3] EEG, CT, MRI and metabolic studies are usually normal initially. EEG pattern, age of onset and initial seizure semiology distinguish Dravet's syndrome from Lennox-Gastaut syndrome[16]. Myoclonic-Astatic Epilepsy (MAE) may be more difficult to distinguish early in the course of the disease[17].

Our patient also showed normal EEG, CT brain, MRI brain, metabolic screen and even MRS scan results. EEG may show slowing and low voltage of background activity. Although EEGs were taken several times, paroxysmal activities were shown multiple times with different patterns of abnormal epileptiform discharges.

It is highly resistant to treatment and seizures persist into adulthood. Poor cognitive development, global delays, behavior problems with hyperactivity, and autistic traits are common[4,5]. Although seizures are intractable, but they are controllable, especially status epilepticus. Newer anti-epileptics have shown promise. These include Stiripentol and Clobazam. Certain drugs including Lamotrigine, Phenytoin, Fosphenytoin, Carbamazepine, Oxcarbazepine and Vigabatrin, are considered to precipitate seizures and they should be avoided.

Developmental assessments should begin as early as possible and should be repeated regularly. Ideally, children with Dravet syndrome should be followed by a neurodevelopmental physician and pediatric psychologist.

Early implementation of global therapies is essential to support optimal development. Children with Dravet syndrome should receive physical, occupational, speech, and social/play therapies and an enriched environment is encouraged[17]. Unfortunately there is no curative treatment for Dravet's syndrome, treatments are merely supportive, as in our case almost all AEDs failed to control the seizures.

The *SCN1A* gene mutation is responsible for most (80%) cases of Dravet's syndrome and 5-10% of generalized epilepsy with febrile seizures plus

(GEFS+) families[18]. Over 300 mutations (missense, nonsense, deletion and splice site) related to dravet's syndromehave been detected in the neuronal sodium channel a1 subunit gene (*SCN1A*)[19,20]. *SCN1A* gene mutation analysis showed mutations in our case also.

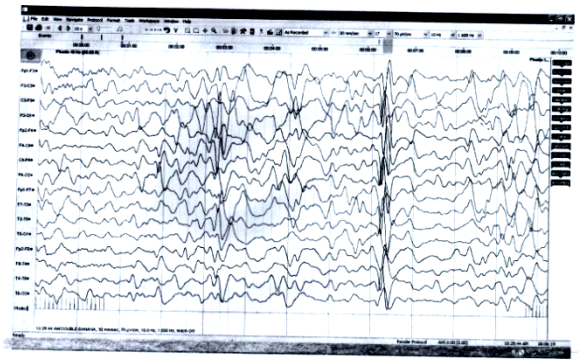

Fig 1: Abnormal Generalized Sharp waves discharge with slow background

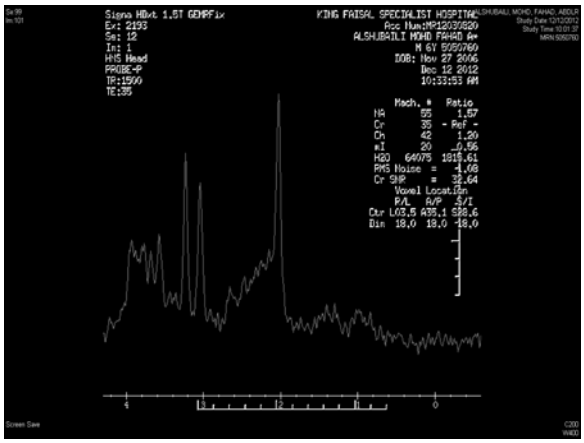

Fig 2: Normal magnetic resonance spectroscopy (MRS) results

It is highly resistant to treatment and seizures persist into adulthood. AEDs may be useful acutely in managing status episodes. Strirpentol and Clobazam have shown some effectiveness in chronic management of seizures. Ketogenic diet has also been used with variable success[21].

In conclusion, Dravet syndrome can be result of several different types of mutation in *SCN1A* gene. Neuro-developmental delay and behavioral problems that appear after two years of age should be expected in all patients as long-term complications of the disease.

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