Drug-resistant epileptic encephalopathy such as Dravet syndrome presents with autistic symptoms. Three cases with autism spectrum disorder with comorbid Dravet syndrome were assessed. All the cases presented with onset of seizures before a year and with autistic features. The patients responded to a combination of antiepileptic drugs (AEDs), resulting in reduced frequency of seizures and behavioral issues. Contrary to the belief that both epilepsy and use of AEDs have adverse impact on the cognition of children with an early onset of epilepsy, we found improvement in the symptoms of our patients who presented with autism and epilepsy. Primary treatment approaches such as occupational therapy, special education, speech therapy, and behavioral therapy; effective diagnosis of comorbidities such as epilepsy; and aggressive treatment might help with behavioral improvement. Early diagnosis followed by treatment with AEDs can improve seizures, electroencephalography abnormalities, and behavioral problems.

**Keywords:** Antiepileptic drugs, autism, Dravet syndrome, epileptic encephalopathy

**INTRODUCTION**

Autism is a neurodevelopmental disorder characterized by social and communication deficits and the presence of restricted interests/stereotyped behaviors. Autistic individuals frequently show associated epileptiform electroencephalography (EEG) abnormalities (prevalence range, 10.3%–72.4%) and epilepsy (prevalence range, 5%–46%). Epileptiform abnormalities may play a causal role in the development of autism as autistic regression is substantially more associated with children with epileptic symptoms.\(^1\)\(^2\)

Epileptic encephalopathies are progressive clinical and electroencephalographic syndromes, where deterioration is thought to be caused by frequent seizures and abundant EEG epileptiform activities.\(^3\) Dravet syndrome (DS), also known as, severe myoclonic epilepsy in infancy is a rare prototype of epileptic encephalopathy, which frequently presents with behavioral symptoms such as hyperactivity and autistic features. It is characterized by febrile or afebrile, generalized or unilateral, and clonic or tonic-clonic seizures, which begin in the 1st year of life in an otherwise apparently healthy infant. It may present with myoclonus, atypical absence, and partial seizures. Developmental delay becomes apparent within the 2nd year of life, and is followed by definite intellectual impairment and behavioral symptoms.\(^4\) Here, we present three cases of autism spectrum disorder (ASD) with the diagnosis of DS, and highlight on a complex interplay between DS and development of autism.

**CASE HISTORY**

**Case 1**

A 4-year-old girl, born of a non-consanguineous marriage, full-term, caesarean delivery, with delayed fine motor milestones, and delayed language development, presented with a history of poor socialization, poor eye contact, no imitation and pretend play, stereotypical movements, repetitive play, and temper tantrums. Her Childhood Autism Rating Scale (CARS) score was 32.5 and Indian Scale for Assessment of Autism (ISAA) was 110. Intelligence assessment using Vineland Social

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Maturity Scale (VSMS) was suggestive of mild mental retardation. (SQ [Social Quotient] = 51). On inquiry, a history of first febrile seizure episode at 4 months of age, and multiple episodes, both febrile and afebrile later, were seen even after starting on syrup valproate. Magnetic resonance imaging (MRI) of brain and EEG did not show any specific abnormality. Pediatric opinion was sought in view of intractable epilepsy, and it was clinically diagnosed as DS. Patient was diagnosed as ASD with DS.

She receives valproate, clobazam, and levetiracetam now, shows improvement in temper tantrums, and her seizures are controlled. On follow-up, her CARS score was 31 and ISAA score was 97.

**Case 2**

A 7-year-old boy, born of a non-consanguineous marriage, full-term, normal delivery, with delayed language development, and normal motor milestones, presented with poor story-telling skills, exaggerated emotions, and repetitive speech. His CARS score was 27 and ISAA score was 72. IQ score using the Seguin Form Board was 58.

The patient had a history of febrile seizure on day 21, and multiple episodes later even on clobazam, but responded well to oxcarbazepine. MRI of brain suggested bilateral hippocampal sclerosis. EEG was suggestive of slow-wave activity in sleep state. Other probable cause for slow-wave EEG in sleep is sleep apnea; sleep deprivation was ruled out. The patient was diagnosed as a case of ASD with DS.

The patient now receives clobazam and oxcarbazepine, and is better behaviorally and his seizures are controlled. Posttreatment CARS score was 27 and ISAA score was 70.

**Case 3**

A 3-year-old girl, born of a non-consanguineous marriage, full-term, normal delivery, with delayed motor milestones, and language development, presented with a history of poor eye contact, not responding when called, not pointing at things, hyperactivity, irritability, stereotyped hand movements, and head banging. Her CARS score was 44.5 and ISAA score was 126. Intelligence assessment using VSMS was suggestive of moderate retardation in social maturity (SQ = 40).

On inquiry, a history of first febrile seizure episode at 3 months of age and multiple episodes, both febrile and afebrile, later were seen even after starting on valproate and phenobarbital. MRI of brain and EEG did not show any abnormality. Pediatric opinion was sought in view of intractable epilepsy, and the patient was diagnosed with DS. The patient was diagnosed as a case of ASD with DS.

The patient now receives valproate, clobazam, and risperidone, resulting in slight decrease in the frequency of seizures, and decreased irritability and head banging episodes. Her posttreatment CARS score was 40 and ISAA score was 116.

**DISCUSSION**

ASDs frequently co-occur with epilepsy. The average prevalence of epilepsy is approximately 12% and reaches 26% by adolescence in children with autism.[3] Severe myoclonic epilepsy of infants, that is, DS, is an epileptic syndrome characterized by febrile or afebrile, generalized or unilateral, and clonic or tonic-clonic seizures appearing in the 1st year of life in previously healthy infants. The EEG readings are often normal at the onset, or might display both generalized and focal abnormalities, without a specific electroencephalographic pattern. So is true about neuroimaging, which is normal almost always. All seizure types are mostly resistant to antiepileptic drugs (AEDs), and status epilepticus is frequent.[4,6] Cognitive development in DS follows a characteristic pattern with slowing of psychomotor development, behavioral disturbances, hyperactivity, autistic traits, and mental retardation after the 2nd year of life. Wolff et al,[4] observed that the frequency of seizures in DS probably constitutes a major risk factor for cognitive impairment and developmental regression. A study by Li et al.[7] suggested that nearly one-quarter of the patients with DS had autism and almost 95% showed mental retardation. It has been proposed that autistic regression is directly caused by epileptiform activity, so ASD is considered as a type of epileptiform encephalopathy.[6]

All the three cases had onset of seizures in the 1st year of life, which did not respond to first-line AEDs, and they presented autistic features with mental retardation and behavioral issues similar to the observation by Wolff et al.[4] and Li et al.[7] All of them had a reduced frequency of seizures and showed behavioral improvement after aggressive treatment with AEDs such as valproate, clobazam, and levetiracetam in the first patient; clobazam and oxcarbazepine in the second patient; and valproate and clobazam in the third patient. A study conducted in Turkey found improvement in autistic features after the treatment with antiepileptics in a child with Landau Kleffner syndrome, which is also a type of epileptic encephalopathy.[8] Similarly, all the three patients showed improvement in hyperactivity
and autistic symptoms after their seizures were controlled with a combination of various AEDs such as valproate, clobazam, oxcarbazepine, and levetiracetam. Nieto Barrera et al.\cite{10} from Spain suggested valproate, topiramate, and benzodiazepines as effective therapeutic options for the treatment of DS.

Contrary to the belief that both epilepsy and use of AEDs have adverse impact on the cognition of children with early onset of epilepsy, we could find improvement in the symptoms of our patients who presented with autism and epilepsy.\cite{11} Although the practice guidelines of the American Academy of Neurology and the Child Neurology Society refrain from recommending an EEG study in all individuals with ASD because of inadequate evidence, advising an EEG may be a good choice than not, if there happens to be a history of clinical or subclinical seizures and a history of delay in the development in infants.\cite{12} Evidence shows that the patients with autism show improvement with primary treatment approaches such as occupational therapy, special education, speech therapy, and behavioral therapy; however, effective diagnosis of comorbidities such as epilepsy and aggressive treatment might help with behavioral improvement.

**Conclusion**

Rapid and aggressive treatment of epilepsy in the children with autism may be associated with better developmental outcomes. The failure to control seizures in persistent epileptiform activity produces regression in the function of central nervous system, resulting in children presenting with ASD symptoms such as restricted interests and repetitive behaviors. Regression in social interaction and language should be carefully assessed via neurological, psychiatric, and audiological examinations, and epileptic syndromes should be considered in the differential diagnosis. Early diagnosis followed by treatment with AEDs can improve seizures and EEG abnormalities.

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**Conflicts of interest**

There are no conflicts of interest.

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