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Epilepsy Characteristics in Duchenne and Becker Muscular Dystrophies

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Abstract

Dystrophinopathies cover a spectrum of X-linked muscle disorders including Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and cardiomyopathy due to pathogenic variants in the *DMD* gene. Neuropsychiatric manifestations occur approximately in one-third of patients with dystrophinopathy. Epilepsy has been described. Here we report seizure and electroencephalographic features of boys with dystrophinopathy and epilepsy. This is a retrospective chart review of eight patients with dystrophinopathy and epilepsy seen at Arkansas Children's Hospital and University of Rochester Medical center. Six patients had DMD and two had BMD. Five patients had generalized epilepsy. Three patients had focal epilepsy and the seizures were intractable in two of them. Brain imaging was available for five patients and were within normal limits. EEG abnormalities were noted in six patients. Seizures were well controlled on the current antiepileptic medication regimen in all patients. Further research is needed to better elucidate the underlying mechanisms and genotype-phenotype correlations.

Keywords

EEG, epilepsy, Duchenne muscular dystrophy

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Introduction

Dystrophinopathies constitute a group of X-linked muscle disorders resulting from pathogenic variants in the *DMD* gene that encodes dystrophin. The clinical spectrum of dystrophinopathy include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and X-linked cardiomyopathy.[1] DMD usually presents in early childhood with delayed motor milestones and weakness. DMD is rapidly progressive, with affected children being wheelchair dependent by the age of 12 years.[1] Cardiomyopathy occurs in almost all individuals with DMD after the age of 18 years. Few survive beyond the third decade, with respiratory complications and progressive cardiomyopathy being common causes of death.[1] BMD is characterized by later onset skeletal muscle weakness. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in BMD.[1] Milder cases of asymptomatic elevation of serum creatine kinase and predominant behavioral problems are not uncommon.[2,3] The central nervous system involvement in dystrophinopathy has been recognized[4,5] but understudied. A wide range of neurodevelopmental disorders, neuropsychiatric comorbidities, and cognitive delay have been reported in boys with dystrophinopathy including attention deficit hyperactivity disorder (12-33%), obsessive compulsive disorder (5%), anxiety/depression (25%), and social challenges.[4–6] Seizures and epilepsy have been reported.[7,8] Here we describe the seizure and electroencephalographic (EEG) manifestations of epilepsy in our patients with dystrophinopathy.

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Search terms: Seizures, epilepsy, intractable, DMD, BMD, Muscular dystrophy.

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Table 1. Demographic and Clinical Information of Our Patients with Dystrophinopathy and Epilepsy.

Patient Number	Current age (years)	Age at diagnosis of dystrophinopathy (years)	Phenotype	Genotype	Steroid therapy
1	24	7	BMD	Diagnosed by muscle pathology	No
2	14	2	DMD	Stop codon (details not available)	Deflazacort
3	11	4	DMD	Exons 46–55 deletion	Deflazacort
4	11	Prenatal	DMD	Exons 45–52 deletion	Prednisone
5	10	1	BMD	Exon 48–51 deletion	No
6	17	10	DMD	Exons 46–51 deletion	Prednisone
7	14	6.5	DMD	Exons 48–54 deletion	Deflazacort
8	16	3	DMD	Stop codon c.1207G>T; p.Gly403*	Deflazacort

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy.

Table 2. Clinical Characteristics of Epilepsy in Our Patients With Dystrophinopathy.

Patient Number	Age at first seizure	Seizure semiology	EEG findings	Epilepsy type	Brain imaging	Current AEDs	Previous AEDs	Status epilepticus
1	6 years	GTCS	NA	Generalized epilepsy	NA	Lamotrigine Clonazepam	None	No
2	13 years	GTCS	2–4 Hz generalized spike and poly-spike wave discharges	Generalized epilepsy	Normal CT	Zonisamide	None	No
3	4 months	NA	Atypical spike and waves discharges in the right occipital region	Focal epilepsy	NA	Levetiracteam	Topiramate	No
4	3 years	Focal seizure	Diffusely slow background for age; Multifocal epileptiform discharges	Focal epilepsy	Normal MRI	Clobazam	Carbamazepine Zonisamide Clonazepam Topitamate	Yes
5	5 weeks	Focal seizure (right arm posturing followed by hyperkinetic movements)	Diffusely slow background for age; right temporal inter-ictal epileptiform discharges	Focal epilepsy	Normal MRI	Vigabatrin Lacosamide	Oxcarbazepine Levetiracetam Phenobarbital Valproic acid Topiramate Lamotrigine	yes
6	14 years	GTCS	Normal	Generalized epilepsy	Normal CT	Levetiracetam	None	No
7	13 years	GTCS	Intermittent generalized spike and poly-spike wave discharges	Generalized epilepsy	Normal CT	None	None	No
8	14 years	GTCS	Fairly frequent generalized spike and poly-spike and wave discharges	Generalized epilepsy	NA	Levetiracetam	None	No

GTCS: Generalized tonic clonic seizure; NA: Not available; CT: Computed tomography; MRI: Magnetic resonance imaging.

Methods

This retrospective study was conducted at Arkansas Children's Hospital and University of Rochester Medical center as approved by the respective institutional review boards. Electronic health records of patients with dystrophinopathy and seizures/epilepsy were reviewed. The following data were collected as available: type of dystrophinopathy, genetic information, seizure and epilepsy type, age at first seizure, EEG findings, neuroimaging findings, seizure control, anti-epileptic medications used, and medical, family, and surgical history.

Results

We included eight patients with dystrophinopathy who had epilepsy. The demographic information is illustrated in table 1 and their epilepsy characteristics in table 2. Six patients had DMD and two had BMD. Five patients had generalized epilepsy. Seizures were intractable (no seizure control after adequate trials of two antiepileptic medications) in two of the three patients with focal epilepsy. There was no head injury prior to first seizure in any of our patients. Brain imaging as available were within normal limits. EEG abnormalities were noted in six patients. Seizures were well controlled on the current antiepileptic medication regimen in all patients.

Discussion

Neuropsychiatric manifestations such as ADHD, learning difficulties, autism spectrum disorder, anxiety, and intellectual disability occur in approximately one-third of patients with dystrophinopathy.[4,6,9,10] Due to recent studies investigating the role of dystrophin in brain function, there is some insights into the extent of dystrophin disturbances resulting in central nervous system manifestations such as seizure disorders. Although epilepsy and DMD have been described before as rare comorbidities, growing evidence suggests the prevalence of epilepsy in dystrophinopathy is more common than previously documented. The prevalence of epilepsy in dystrophinopathy is estimated to be from 3.14% to 8% which is substantially higher than that of in the general population (0.5-1%).[7,8] Several seizure and epilepsy types have been described in patients with DMD and BMD. Generalized epilepsy consisting of generalized tonic- clonic seizures, and absence seizures were more common. Focal epilepsy has also been reported.[7,8] In our cohort, 5 patients had generalized epilepsy and three had focal epilepsy. None of our patients had absence seizures.

Dystrophin aids in the anchoring and stabilization of GABA receptors as well as in regulation of neurotransmitter release.[11] The *DMD* gene encodes various dystrophin isoforms that are expressed in the central nervous system. The full-length isoforms (3 variants of Dp427) are present in the GABAergic synapses in the cerebral cortex, cerebellum and hippocampus and the shorter isoforms are localized in the glia (Dp260, Dp140, Dp116, and Dp71).[8,12,13] These dystrophin isoforms have been postulated to have possible role in epileptogenesis with varied mechanisms related to their distribution in the brain. The relationship between absence of dystrophin brain isoforms and increased neuronal excitability has been described in animal models.[14,15] Mouse model of temporal lobe epilepsy had shown relationship between dystrophin expression and post-synaptic GABAergic neuronal upregulation.[14] Absence of shorter dystrophin, especially Dp71, causes alterations in the aquaporin-4 levels that has been suggested to cause neuronal hyperexcitability and seizures.[8,16] Majority of patients described in this report harbor deletions in *DMD* gene involving shorter dystrophin isoforms.

Studies have shown nonspecific EEG abnormalities such as 14 and 6 Hz positive spikes in patients with dystrophinopathy.[17] These changes could be attributed to functional neural deficits and synaptic dysfunction secondary to absence of dystrophin.[17,18] Such nonspecific EEG changes in the absence of clinical seizures in these boys should be interpreted with caution. None of our patients had these non-specific changes.

In conclusion, we describe the seizure and EEG characteristics of eight patients with dystrophinopathy who also had epilepsy. Further larger studies are needed to better understand the epilepsy characteristics and management, underlying seizure mechanisms, and DMD genotype – seizure phenotype correlations.

Declaration of Conflicting Interests

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