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Epilepsy in dystrophinopathies: A retrospective cohort and review of the literature

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ABSTRACT

Objective: This study aimed to assess the prevalence and characteristics of epilepsy in dystrophinopathies within a cohort of 142 patients at a tertiary neuromuscular center in Istanbul, Turkey.
Methods: We recorded the age at seizure onset, seizure type, family history, history of febrile seizures, treatment, and EEG results. Epilepsy was classified according to the latest International League Against Epilepsy (ILAE) classification.
Results: Of the 142 DMD patients, 8 experienced epileptic seizures (5.6 %). The median age of the patients was 11 years (8.0–15.2). The median age for the first DMD symptoms was 24 months (16.5–37.5). All seizures were consistent with generalized tonic-clonic seizures. Three patients are currently on anti-seizure medication.
Significance: The prevalence of epilepsy in our study (5.6 %) exceeds that of the general pediatric population (0.5–1 %). However, the frequency of febrile seizures in children with dystrophinopathy is similar to that of the general population.

1. Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder resulting from mutations in the dystrophin gene. Common symptoms include progressive skeletal muscle weakness and cardiac involvement.

DMD is the predominant muscular dystrophy in the pediatric population, affecting one in 5,000 live male births. Mutations either result in the absence of dystrophin or disrupt its expression. Becker Muscular Dystrophy (BMD) represents a milder form of dystrophinopathy, characterized by later-onset muscle weakness and cardiac involvement.

Dystrophin is crucial in the central nervous system (CNS) as it's present in both brain and muscle tissues. DMD's impact isn't limited to muscle function. Previous studies have reported increased occurrences of epilepsy and febrile seizures in dystrophinopathies [1–3]. DMD children can also exhibit attention deficit and hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and learning disabilities, such as dyslexia [4,5].

This study aimed to evaluate the prevalence and clinical characteristics of epilepsy in 142 DMD patients from a tertiary neuromuscular center in Istanbul, Turkey.

2. Material and methods

The data was analyzed from 142 DMD patients at the Child Neurology Department of Istanbul Faculty of Medicine, in Istanbul, Turkey. Genetic evaluations, including searches for exon deletions and duplications, were conducted using Multiplex Ligation-dependent Probe Amplification (MLPA). Mutation naming followed the Leiden Muscular Dystrophy database nomenclature, as outlined in the 2000 Human Mutation publication.

Age at onset of seizures, type of seizures, family history of seizure, history of febrile seizure, treatment, and EEGs were recorded. Epilepsy was classified using the recent International League Against epilepsy (ILAE) classification [6]. For clinical severity of DMD, the Gross Motor Function Classification System (GMFCS) scores were used [7].

Ethical approval was obtained from the ethics committee of Istanbul Faculty of Medicine, Istanbul, Turkey.

2.1. Statistical analysis

Descriptive statistics, such as mean and median age at first symptom and DMD diagnosis were determined. The differences in proportions between epilepsy and non-epilepsy groups were examined using Mann

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Whitney *U* test SPSS (version 25) facilitated statistical analyses.

3. Results

Our cohort consisted of 142 patients with DMD and BMD. No BMD patients were epileptic. The median age of the patients was 11 years (8.0–15.2). The median age of first DMD symptoms was 24 months (16.5–37.5). The mean follow-up period of the patients was 8.8 ± 5.2 years. Clinical and follow-up of patients with DMD and epilepsy were summarized in Table 1.

Epileptic seizures were found in 8 of the 142 DMD patients (5.6 %). The mean age of first seizure was 31.8 ± 26.8 months. Preliminarily, febrile seizures occured 5 of the patients. There is one another patient who had single simple febrile seizure except the cohort. The prevelance of the febrile seizure in DMD patients was 4.2 % (n = 6). Of the patients with febrile seizures, 3 had complex febrile seizures and developed epilepsy during follow-up. None of the patients with epilepsy had risk factors for epilepsy for instance head trauma, hypoxic encephalopathy or infections. None had a family history of epilepsy. The predominant seizure type was generalized tonic-clonic seizure and seizures manifested as unprovoked seizures. Although the seizures occurred as unprovoked seizures, febrile seizures were also observed in 6 of the patients. There are no patients with focal seizures. From the perspective of epilepsy classifications, this type is considered unclassified epilepsy with generalized tonic-clonic seizures, despite not fitting any childhood epilepsy syndromes based on clinical and electrophysiological findings.

Considering the EEG abnormalities, two of the EEGs showed generalized high voltage 3 Hz spikes over the posterior regions. EEG examination was within normal limits in five of the patients. Furthermore, the epilepsy of the patients did not belong to any of the ILAE epilepsy syndrome subgroups. When the genetic analyzes of the patients were examined, the deletions were different from each other. Exon 48–49 and 49–54 deletions were detected in patients followed up with febrile seizures. Other patients had deletions between exon 43 and exon 57.

Notably, three patients are currently on anti-seizure medication, with Levetiracetam being the chosen drug. Although carbamazepine, phenobarbital, and levetiracetam are used for anti-seizure treatment, patients receiving phenobarbital are found to be seizure-free even after discontinuation of the treatment. According to Table 1, the fourth patient experienced recurrent generalized seizures after febrile seizures and was treated with rectal diazepam and phenobarbital. However, there were no seizures reported after 3 years, and the patient did not experience any further seizures even after discontinuing the anti-seizure drug treatment.

In order to determine the severity of the dystrophinopathy phenotype, patients were examined according to the gross motor function scale. While the median GMFSC scores of patients diagnosed with epilepsy was 2, it was the same as the non-epilepsy group.

4. Discussion

The role on dystrophin stabilization of Gamma-Aminobutyric Acid (GABA) receptors and its role in regulating neurotransmitter release is pivotal. The DMD gene produces several dystrophin isoforms found in the CNS. Full-length isoforms (Dp427 variants) are found in GABAergic synapses in the cerebral cortex, cerebellum, and hippocampus, while shorter isoforms (Dp260, Dp140, Dp116, and Dp71) are localized in glial cells [8–10]. The lack of some isoforms, such as Dp71, may compromise the blood–brain barrier, leading to increased neuronal excitability [11].

Among the dystrophin gene mutations, large deletions are detected in 65 % of cases, duplication in 5 % and point mutations in the rest [12]. In children with Duchenne muscular dystrophy, no point mutation or duplication was detected in this study.

Dystrophinopathies are strongly associated with central nervous system manifestations. In the literature, febrile seizures in 4–15 % and epilepsy in 3–8 % of patients with dystrophinopathy have been reported [1,3,13]. These findings point that epileptic seizures are not a rare condition in DMD. The prevalence of epilepsy in this study (5.6 %) was higher than in the general pediatric population, (0.5–1 %) [14] and similar with the previous studies reporting epilepsy in dystrophinopathies [1,2]. Attention deficit and hyperactivity disorder (11.7 %), ASD (3.1 %) and reading problems can be seen together in patients with DMD [4]. Although comorbidities such as ADHD and ASD have been studied in epilepsy patients with dystrophinopathy in the literature, it has also been reported that these comorbidities in childhood epilepsy [15,16].

The most common seizures in childhood are febrile seizures and their incidence is 2–5 % [17]. It is known that there is an increase in the frequency of febrile seizures in children diagnosed with cerebral palsy and neurodevelopmental disorders [18,19]. In children with dystrophinopathy, the frequency of febrile seizures is 8 % [20]. In this study, the frequency of febrile seizures in children with DMD was found to be 4.2 %, although it was lower than those reported in the literature, but similar to the general population frequency.

Epilepsy was reported more frequently in DMD patients. This observation suggests that reduced brain dystrophin levels may facilitate neuronal excitability [21]. Within the brain, dystrophin is mainly found in the hippocampus, prefrontal cortex, and cerebellum [21]. Other major brain structures, such as the thalamus, hypothalamus, basal ganglia, most of the brainstem, and spinal cord, appear to be devoid of dystrophin [21].

Although patients with mutations between exons 44 and 63 have an increased risk of epilepsy, no causal relationship has been found

Table 1
Clinical and follow-up findings of patients with Duchenne muscular dystrophy and epilepsy.

Patient no.	Age at 2022 (yr)	Age at onset of seizures	History of febrile seizure	Family history of epilepsy	Genetics	Seizure type	EEG	Treatment	GMFSC
1	13 yr	5 yr	No	No	del. 48–49	Generalized	Generalized epileptiform abnormality	LEV	1
2	9 yr	12 m	Yes	No	del. 45–50	Generalized	Theta waves	PHB	2
3	24 yr	7 yr	No	No	del. 49–54	Generalized	N	LEV	5
4	10 yr	18 m	Yes	No	del. 42–43	Generalized	N	–	2
5	9 yr	12 m	Yes	No	del. 45–54	Generalized	N	LEV	2
6	13 yr	3 yr	Yes	No	del. 47–50	Generalized	Generalized epileptiform abnormality	LEV	2
7	15 yr	2 yr	Yes	No	del 23–44	Generalized	N	CBZ	1
8	8 yr	12 m	No	No	del. 45–57	Generalized	N	PHB	1

EEG: Electroencephalography, **GMFSC:** Gross Motor Functional Classification System, **LEV**: levetiracetam, **PHB:** phenobatbital, **CBZ:** carbamazepine.

between a particular mutated exon and the occurrence of epilepsy [3]. Epilepsy occurred in 3.7 % of patients with exon 31 mutations, and 7.5 % of patients with mutations between exons 31 and 62 [3]. In our cohort, the mutations in patients diagnosed with epilepsy are between exon 27 and 57. Epilepsy in DMD patients was linked to mutations upstream of exon 62, affecting key dystrophin isoforms, particularly Dp427 [5]. One study noted an up-regulation of Dp427 in temporal lobe epilepsy, suggesting a failed response in DMD patients to control brain hyperexcitability, potentially increasing epilepsy susceptibility [5]. However, the rarity of mutations affecting the Dp71 isoform, alongside the small number of patients with both DMD and epilepsy, limited the scope for conclusive analysis.

There is no consensus in the literature on seizure types. Goodwin et al. reported generalized tonic-clonic, 1 absence (and generalized tonic-clonic) and infantile spasm in 1 of 8 dystrophinopathy patients [1]. Pane et al. found focal seizures in 6 patients, generalized tonic-clonic seizures in 4 and absence seizures in 4 of 14 dystrophinopathy patients [3]. Hendriksen et al. reported 36.8 % (n = 7) absence, 31.6 % tonic-clonic (n = 6) and 31.6 % (n = 6) focal seizures [5]. Ramani et al. followed 8 children with dystrophinopathy with generalized tonic-clonic seizures in 5 and focal seizures in 3 patients [22]. In three patients, the coexistence of West syndrome and DMD was reported at the case level [23,24]. Although all of the patients in our study were followed up with generalized tonic-clonic seizures, it makes an important contribution to the diversity in the literature. Contrary to what has been reported in the literature, epilepsy has not been detected in patients with Becker muscular dystrophy [1,22]. The fact that most of the patients had a history of febrile seizures, that their seizures were generalized tonic-clonic seizures, and that the electrophysiological findings were not diverse made it difficult to classify them in terms of an epilepsy syndrome diagnosis. However, it emphasizes the necessity of repetitive EEG examinations in follow-up and suggests that there may be genetic generalized epilepsy syndrome in later ages.

Although generalized tonic-clonic seizure type was dominant in our patient group, focal seizures were not observed. All 3 patients receiving anti-seizure medication are followed without seizures. During the follow-up period of 8.8 years, refractory epilepsy was not observed in the patients with dystrophinopathy. Additionally, some patients were able to discontinue their treatment after a certain period of time, indicating that epilepsy in children with dystrophinopathy may have a self-limiting feature.

Seizure management in patients with dystrophinopathy is important in terms of aspiration risk and clinical outcome of the disease, especially in the respiratory muscle involvement stage. The fact that seizures were mostly controlled with a single anti-seizure medication and that status epilepticus was not reported in the literature suggested that it would not affect the course of the disease. Levetiracetam can also be considered as a preferred option due to its easy availability and useful option in controlling seizures beside the GABAergic drugs. The clinical course of dystrophinopathy was not affected by epilepsy as indicated by similar GMFCS values in children with and without epilepsy.

One of the limitations of our study is that it is a retrospective study. Another limitation is that several of the children are young and have to follow up for diagnosis of epilepsy. The strength of the study is that it provides information that will contribute to the literature with the frequency of epilepsy and seizure types in dystrophinopathy patients, and the understanding that febrile seizures are similar to the general pediatric population.

5. Conclusion

Dystrophin deficiency is believed to heighten neuronal excitability by influencing neurotransmitter receptors and cellular ion channels. Therefore, it has resulted in an increase in the frequency of epilepsy in dystrophinopathies compared to the general pediatric population. Presently, no study has conclusively linked a specific type of deletion with seizures or CNS involvement. As our understanding of dystrophinopathies expands, we realize that it is not only a neuromuscular condition, but also a CNS-related group of disease. Thus, the role of dystrophy in epileptogenesis, potential treatments, and the need for more research on disease phenotyping are emphasized.

CRediT authorship contribution statement

Özgü Kizek: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Visualization, Project administration, Resources, Writing – original draft, Writing – review & editing, Validation. **Zuhal Yapıcı:** Conceptualization, Supervision. **Pınar Topaloğlu:** Conceptualization, Methodology, Data curation, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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