Original Article

Epilepsy in Boys with Duchenne Muscular Dystrophy

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Abstract

Background: Regarding the unexpected frequency of epilepsy in patients with Duchenne Muscular Dystrophy (DMD), this study was conducted to assess the impression of Duchenne - related epilepsy.

Methods: After definite diagnosis of DMD in 57 children attended to neurology clinics, a questionnaire including demographic variables and data related to symptom presentations was completed for each one. If history of epilepsy was present, complementary information on the background of epilepsy (based on history taking and Paraclinical data) was obtained.

Results: Among 54 patients with DMD, seven cases (12.3%) had the history of epilepsy versus 0.4 - 0.5% in general population ($p<0.001$). Known causes of epilepsy were ruled out in these patients. From 7 patients with epilepsy, 6 cases had mild mental retardation and one of them had normal mental status.

Conclusion: Our data suggests that epilepsy may be a rare associated feature of DMD. Absence of dystrophin in the central nervous system (CNS) may cause suppression of inhibitory synapses in cortex and hypocampus which in turn brings epileptic foci into play.

Keywords: Epilepsy, Duchenne Muscular Dystrophy (DMD), Dystrophin.

Duchenne Muscular Dystrophy (DMD) is an X - linked recessive disease and has the second highest incidence of all inherited diseases, approximately one in 3300 live male births[1]. The disease presents as muscle weakness that is first apparent at 3-4 years of age. Pathologic studies have demonstrated that muscle weakness is due to an irreversible, ongoing loss of skeletal muscle which is due to a mutation in dystrophin gene and absence of dystrophin is the main cause of the disease[2, 3]. Except isoforms present in skeletal muscle, there are also different isoforms expressing in cardiac muscle, retina, kidney and also central and peripheral nervous systems[4, 5]. In several studies on animal models, neuron reduction and degeneration in cortex and brain stem have been demonstrated. In boys with DMD, elevation of choline containing compounds, reflecting CNS pathology is reported, also electroencephalography (EEG) abnormalities and synaptic function disturbences in the absenc of dystrophin have been described[6]. A significant proportion (35%) of children with DMD suffer from non-progressive mental retardation, cognitive impairment, and psychiatric symptoms[7]. Although there are many researches about mental retardation as a on CNS complications in DMD, there are few reports[7] on seizure in this disease.

Regarding the unexpected frequency of epilepsy in patients with DMD in our study area, this research was conducted to assess the impression of Duchenne - related epilepey to aid having a better view on this issue.

Materials and Methods

All children with the impression of DMD who were referred to three neurology clinics in Isfahan, whose neurologist was the author of this article, from september 1997 to 2002 were studied. The inclusion criteria included:

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1. Remarkable proximal muscle weakness in a male patient before 5 years of age and inability to walk before 15 years of age.
2. The serum level of Creatine Phospho Kinase (CPK) more than 1000 IU at the time of diagnosis.
3. Electromyography (EMG) study suggesting myopathy.
4. Confirmed diagnosis of DMD through muscle biopsy.

Patients who met all these criteria were included into the study.

Laboratory tests were done in the same laboratory for all cases and the same pathologist performed pathologic examinations. EMG was performed according to the method described by Toennies.

Demographic variables, onset of symptom presentation, family history of muscular diseases, physical findings suggesting the diagnosis, the level of CPK at the time of diagnosis, EMG report, Intelligence Quotient (IQ), growth profile and presence of epilepsy were recorded in a questionnaire for all patients by the neurologist.

The IQ for children was evaluated with Wechsler test and recorded as normal (>70), mild (40-70), moderate (25-40) or severe (< 25) mental retardation (MR)[8].

In patients with reported epilepsy, another questionnaire with the following information was also completed: The age at which the first episode of epilepsy was experienced, the sequence of seizure and muscular symptom presentations, the sequence of seizure and diagnosis of DMD, the frequency of seizure up to now, type of seizure (based on history taking), history of febrile seizure, other cerebral pathologies (based on history taking, CT scan and MRI) perinatal problems such as asphyxia and jaundice (on the basis of history taking and the mothers' delivery record) and the pattern of EEG. EEG for all cases was recorded with Nihon Kohden (model: Neurofax) and interpreted by the same neurologist.

The findings were presented as mean ± SD for quantitative variables and n (%) for qualitative ones. The relative frequency of epilepsy between study group and overall population with the same age was compared with Z - Test. The significance level was considered to be less than 0.05. Statistical analysis was performed with SPSS 11.0 software.

Results

In this study 57 subjects who met the criteria for DMD were studied. The age of children at the onset of symptoms (proximal muscle weakness) was 3.5 ± 0.7 (range: 2-5 yr). In 24 cases (57.9%) the family history of muscular disease was positive. Evaluating the patients' IQ revealed that in 42 cases (73.7%) the level of IQ was in the normal range and 15 patients (26.2%) suffered from mild MR which was significantly higher than the value in population of the same age range (P<0.001). Moderate or severe MR was not detected.

Assessment of growth curves showed that all children were in the normal range. In study population seven cases (12.3%) had experienced epilepsy which was much more than overall prevalence of epilepsy (0.4-0.5%)[9] in the same age group (p<0.001). From 7 subjects with epilepsy 6 cases suffered from mild MR. In patients with history of epilepsy complementary data were as follows: The age of first epilepsy was 8.5 ± 1.7 years (range: 6-11 year). In all cases these episodes happened after the onset of muscular symptom presentations and definitive diagnosis of Duchenne disease. In the period between onset of DMD and data collection, the frequency of seizure was 3.6 ± 1.7 episodes (range: 2 – 6 episodes); In other words, patients had experienced approximately one episode of seizure per year. On the basis of history, epilepsies were limited to generalized tonic – clonic (6 cases) and secondary generalized (1 case) types. All patients were properly under control with routine antiepileptic medications. None of the patients had the history of febrile seizure. In addition, family history of seizure unrelated to fever was negative. With respect to history taking, CT scan, MRI (All the seven cases with epilepsy were screened with brain MRI, but brain CT scan was done on three most suspicious cases) and prior medical records, other cerebral pathologies responsible for seizure were ruled out. Also perinatal problems such as asphyxia were ruled out based on history taking and medical records.

Discussion

In this study, the prevalence of epilepsy in children with DMD was 12.3% which was significantly higher than general population in the same age group[9]. Also in the only similar survey, the prevalence of epilepsy in patients with DMD and Becker

disease was reported more than normal population but no explanations presented[7]. In order to find a plausible explanation of our finding, i.e. higher prevalence of epilepsy in DMD patients, we should look through DMD pathogenesis.

DMD is the result of a mutation in dystrophin gene and dystrophin is a membranous protein located in the inner surface of plasmalema[3]. Other than its known role in skeletal muscle, it's role in some other tissues such as cortex, hypocampus and cerebellum has also been described which has colocalization with GABA-A receptor in some inhibitory synapses[10].

It has been speculated that a possible role of dystrophin in the brain is anchoring or clustering and stabilization of GABA-A receptors[11, 12]. Dystrophin forms a link between the cytoskeleton and the extracellular matrix and in the absence of dystrophin, a reduction in size and number of GABA-A receptors is said to take place[13].

GABA receptor is one of inhibitory receptors of brain and the suggestion that reduction in GABA-ergic inhibition causes acute seizure has been proposed since some years ago. This idea originates from the known role of GABA - mediated inhibitory drugs in controlling epilepsy[14]. This hypothesis is generally based on animal models and has not been completely accepted in human being[15].

According to prior discussed impressions, we can hypothesize that reduction in GABA-A receptors in Duchenne may eliminate its inhibitory role on epileptic discharges and this in turn would result in increasing the risk of epilepsy in these patients.

In this study, 26.2% of children had mild MR which shows a significant difference with the overall prevalence of MR in general population (1-3%)[16]. There are several studies available on cognitive disorders and IQ in DMD; for instance the reported prevalence of MR in one research is 35%[7] and it is estimated that the mean IQ of children with DMD is approximately one SD lower than general population[6]. In order to explain these findings some hypotheses are already present. For example it is said that the absence of dystrophin results in glucose hypometabolism and disturbances in regulating oxidative metabolism in hypoxic situations[12, 17]. There is much evidence that GABA-A receptor, potentiates tolerance to hypoxic situations[18]. Regarding the role of GABA-ergic receptors in the pathophysiology of DMD, intolerance of cerebral cells to hypoxia may be somewhat explained. In addition, rapid and shallow pattern of breathing in Duchenne induces chronic hypercapnia which may affect brain energy metabolism[6].

With respect to the accepted role of hypoglycemia[19] and hypoxia[20] in precipitating seizure, and accompaniment of MR and epilepsy in most of our patients, some other explanations can be considered for increased risk of epilepsy in Duchenne disease. In other words, in addition to GABA-ergic hypothesis, some mechanisms such as altered glucose metabolism and loss of cellular accommodation to hypoxia may have a role in predisposing patients into epilepsy.

Further investigations with larger sample size and more meticulous focus on the background of epilepsy in patients with DMD are suggested.

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