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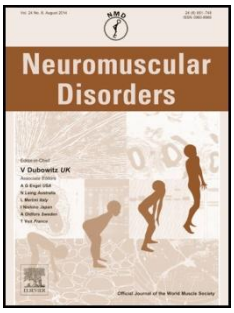

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DMD and West Syndrome

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HIGHLIGHTS

1) West syndrome and Duchenne Muscular Dystrophy
2) Spectrum of seizure types in DMD patients
3) Treatment of seizure in DMD patients
4) Dystrophin and seizure in DMD patients

Abstract

Duchenne Muscular Dystrophy (DMD) is the most frequent muscular dystrophy in childhood, with a worldwide incidence of one in 5000 live male births. It is due to mutations in the dystrophin gene leading to absence of full-length dystrophin protein. Central nervous system involvement is well-known in Duchenne Muscular Dystrophy. The multiple dystrophin isoforms expressed in brain have important roles in cerebral development and functioning. The association of Duchenne Muscular Dystrophy with seizures has been reported, and there is a higher prevalence of epilepsy in Duchenne Muscular Dystrophy patients (between 6.3% and 12.3%) than in the general pediatric population (0.5-1%). Duchenne Muscular Dystrophy patients may present with focal seizures, generalized tonic-clonic seizures or absences. We report on two boys in whom Duchenne Muscular Dystrophy is associated with epileptic spasms and hypsarrhythmia that fulfil the criteria for West syndrome, thus extending the spectrum of seizure types described in Duchenne Muscular Dystrophy patients.

Keywords: Duchenne muscular dystrophy; dystrophin; West syndrome; seizures

1. Introduction

Duchenne muscular dystrophy (DMD, MIM # 310200) is an X-linked recessive condition affecting approximately one in 5000 live male births (1). It is caused by mutation in the *DMD* gene (MIM # 300377) that leads to the absence or disruption of expression of the protein called dystrophin, found in a variety of tissues including skeletal and cardiac muscle and the central nervous system (CNS). A number of transcripts are produced from the *DMD* gene; these encode various dystrophin isoforms, some of which are expressed in the brain. Among the dystrophin protein variants expressed in the nervous system, two are of main interest. Dp140 is a distal dystrophin isoform mainly expressed during fetal development that is detected throughout the CNS, in cerebral cortex, cerebellum, hippocampus, brain stem, and spinal cord. Dp71 is a ubiquitous dystrophin isoform also found in the brain, and mutations that alter Dp71 production are thought to be responsible for the most severe cases of intellectual disability in DMD patients (2). A significant proportion of children with DMD suffer from non-progressive cognitive impairment (3), accompanied by specific learning and behavioral disabilities such as automatization of reading, attention processes, and expressive language skills. Deletions at the 3' end of *DMD* are associated with a higher incidence of cognitive impairment. DMD boys were found to display electroencephalogram (EEG) abnormalities in some studies (4), suggesting that synaptic function could be affected by the absence of dystrophin in the brain.

West syndrome is an epileptic encephalopathy that involves a specific pattern of seizures known as epileptic spasms, hypsarythmia on EEG and psychomotor regression. The incidence of West Syndrome is estimated between 1:4.000 and 1:6000, with peak incidence between 4 and 6 months of age (5). The main treatments are hydrocortisone or adrenocorticotropic hormone (ACTH) and vigabatrin. We present here the clinical,

electrophysiological, and therapeutic aspects of two boys affected by DMD and West Syndrome. This study enlarges the spectrum of epilepsy syndromes correlated with DMD.

2. Case report

2.1. Case #1

This 2-year-old boy is the only child of Russian non-consanguineous parents. No family history of DMD or epilepsy was present. After a pregnancy marked by seroconversion by CMV and full-term-birth, the child developed epileptic spasms at the age of 5 months, with no psychomotor regression. Brain MRI was normal as well as metabolic tests including lactate in blood and CSF and amino acids in the blood. The EEG revealed a pattern of hypsarrhythmia (Figure 1A). Hydrocortisone was added 6 months after unsuccessful treatment with vigabatrin, topiramate, clobazam and prednisone. Addition of hydrocortisone resulted in an immediate improvement with the total control of spasms and the normalization of the EEG. Systematic blood tests showed elevated transaminase and creatine kinase levels of 12000 U/l. At 18 months, the patient's *DMD* gene was sequenced, revealing a large out-of-frame deletion encompassing exons 8 to 16, thus confirming the diagnosis of DMD. There was no psychomotor regression noticed, with walking acquired at 15 months. The child was kept on hydrocortisone treatment starting by 10 mg/kg/d then decreasing over 11 months and was free of spasms from the age of 12 months.

At 24 months, hydrocortisone was replaced by deflazacort at 0.5 mg/kg/day. At the most recent clinical examination at the age of 24 months (Figure 1B) weight, height, and head circumference indicated a harmonious growth curve. The child presented with some unusual facial features: large forehead, flattened nasal bridge, widely spaced teeth,

and anteverted nostrils. There was an important calf hypertrophy; no retractions and no scoliosis were found. Walking was possible, but the child had poor coordination. Positive Gower's sign was reported. Cognitive development was mildly delayed; the patient did not speak in sentences but had a good comprehension of words. Vigabatrin was stopped at the age of 3 years old. He has been free of spasms for over 3 years at the writing of this paper. EEG at 24 months showed a slight background rhythm asymmetry with a few slow waves in left central derivations. Repeated MRI revealed no abnormality. A molecular study analysis did not reveal any punctual mutations or large rearrangements in a series of genes implicated in epileptic encephalopathies. The screening of the whole coding regions of *CDKL5*, *IQSEC2*, *MBD5*, *MEF2C*, *SLC9A6*, *STXBP1*, *UBE3A* and *ZEB2* genes was performed using Ampliseq approach and PGM Life Technologies sequencers. Only a heterozygous missense variant c.1382G>A (p.Arg461His) in *MBD5* gene was detected. This variant was reported in the ExAC database (rs139964770; 47 / 120,214) in unaffected individuals and was also found in the father's DNA, which renders the possibility of an epileptic encephalopathy due to MBD5 gene variant rather unlikely in this patient.

2.2. Case #2

This boy is the second child of a Romanian non-consanguineous family. There was no family history of DMD or epilepsy. Pregnancy and birth were uneventful. At 4 months and 3 weeks, the child presented with paroxysmal events consisting of clusters of sudden symmetric flexion movements of trunk and limbs; these events occurred shortly after awakening. At a medical examination at the age of 5 months, epileptic spasms were identified as well as a global developmental delay with inconsistent social smile. No apparent regression was notified. Clinical evaluation showed normal harmonious growth in weight, height, and cranial circumference curves. No constitutional features

and no achromic spots were noticed. A neurological and developmental evaluation revealed axial hypotonia with normal deep tendon reflexes. The EEG showed a pattern of symmetric hypsarrythmia. Brain MRI was normal. Creatine kinase levels were higher than normal at 6590 UI/l. Sequencing of the *DMD* gene showed a point mutation in exon 10 that results in a nucleotide substitution in position 1006 leading to a premature stop codon c.1006G>T, p.(Glu336*)(NM_004006.2). The ACTH Synacthene was started at a dose of 0.5 mg/kg every other day for 2 weeks, with progressive tapering after that; total duration of Synacthene treatment was approximately 6 weeks. Cessation of epileptic spasms and disappearance of hypsarythmia on EEG were noticed beginning with the second dose of Synacthene. The patient has been free of epileptic spasms since the age of 6 months and has not received any chronic treatment after completion of the Synacthene scheme. He began to walk independently at 16 months. At the most recent clinical evaluation at the age of 21 months, his weight, height, and head circumference were average. Cognitive developmental age was delayed by about 9 months, and the child was very active. No pathogenic variant was detected in the whole coding regions of *CDKL5*, *IQSEC2*, *MBD5*, *MEF2C*, *SLC9A6*, *STXBP1*, *UBE3A* and *ZEB2* genes using Ampliseq approach and PGM Life Technologies sequencers.

3. Discussion

In this report we describe two boys with typical West syndrome associated with Duchenne Muscular Dystrophy. An association between muscular dystrophies and epilepsy has already been reported (6). The prevalence of epilepsy in DMD patients is estimated from 6.3% to 12.3% higher than in general pediatric population (0.5-1%) (7). This could be due to the fact that some dystrophin isoforms, namely Dp427(B), Dp140, Dp71are expressed throughout the brain, and their dysfunction may impact neuronal excitability contributing to generation of seizures (8). Seizures are more often focal,

generalized tonic-clonic, or absences. Cognitive and behavioral disabilities, such as autistic traits, hyperactivity, and intellectual disability , are reported mostly in children with mutations in the distal part of the *DMD* gene (4); these patients are also likely to have cerebral abnormalities detectable by MRI (9, 10).

The association between absence of dystrophin brain isoforms and increased neuronal excitability was previously reported in animal models. There is also experimental evidence for a potential role of brain dystrophin in seizure generation(11). Dystrophin has a role in the anchoring and stabilization of GABA receptors, as well as in regulation of neurotransmitter release and it is well known that abnormal GABAergic synaptic transmission contributes to seizures (12).

Theoretically, West syndrome and DMD could be associated due to a large deletion involving *DMD* and *ARX* genes (13). *ARX* is a gene located on Xp22.13 close to dystrophin (Xp21.2). Mutations in *ARX* result in severe epileptic encephalopathies in boys, including West syndrome.

Both patients described here have had rather favorable outcomes, with rapid cessation of seizures and mild cognitive delay at the last follow up with repeated MRI examinations which failed to show any cortical malformations.

As both mutations were located in the proximal part in the *DMD* gene, the DP71 isoform is not involved here. Therefore we considered rather unlikely the possibility of epileptic encephalopathies gene mutations in our patients. The absence of obvious cause of the West syndrome and the rapid response to treatment makes the hypotheses of cryptogenic West syndrome likely.

Despite the high incidence of epilepsy in DMD, the occurrence of West syndrome could constitute a random association. Further reports of this association may confirm that West syndrome expands the spectrum of epilepsy in DMD. An additional interest of the first case described is that long-term follow up of a child treated before 6 months of age with steroids will shed light on the effects of early treatment of DMD patients.

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Conflicts of interest: none

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Figure 1. (A) Electroencephalography of case #1 performed at diagnosis which shows high amplitude asymmetrical slow waves appearing in central left derivations. Also, there are no frequency and no amplitude gradients, indicating a highly disorganized brain activity. (B) Patient #1's appearance at the age of 2 years. Note the mild facial dysmorphism with flattened nasal bridge, widely spaced teeth, and anteversed nostrils.