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Triple Trouble: A Case Report of an Unusual Combination of Duchenne Muscular Dystrophy, Epilepsy, and Autism

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Abstract

We present a 4 year-old boy with an unusual combination of an inherited neuromuscular disorder-Duchenne muscular dystrophy, epilepsy and autism. The patient underwent an extensive clinical, biochemistry, molecular genetics, electrophysiological, and psychological examinations. We discuss a role of dystrophin expression and deficiency in both muscle and brain tissues in the pathophysiology of these disorders. An association between Duchenne muscular dystrophy and autism spectrum disorders has already been described, but this unusual phenotype, including DMD, epilepsy, and autism, has not been reported as yet. We postulate that this "triple trouble" is not a coincidence, but more likely a result of the same underlying process–the dystrophin deficiency.

Keywords: Duchene muscular dystrophy; DMD; Dystrophin; Dystrophinopathy; Neuromuscular disorders; Epilepsy; Autism; Autism spectrum disorders

Abbreviations:

DMD: Duchenne Muscular Dystrophy; MLPA: Multiplex Ligation-dependent Probe Amplification; VEEG: videoEEG; CDKL5 gene: Cyclin-Dependent Kinase-Like 5 Gene; ARX gene: Aristaless Related Homeobox Gene

Introduction

Duchenne and Becker muscular dystrophies (DMD/BMD), commonly known as dystrophinopathies, are an X-linked progressive neuromuscular disorders, caused by the absence of protein dystrophin due to a mutation in the dystrophin gene (DMD gene)–the largest gene in the whole human genome with 79 exons. Dystrophin is a large protein that can be found in muscles. It is more highly concentrated in skeletal and cardiac muscle, less in smooth muscle. The only non-muscle tissue, which expresses substantial quantities of dystrophin is the brain, where we can found about 10% of the level found in the skeletal muscle [1].

DMD has a prevalence of 1 in 3500 live male births [2]. Symptoms of DMD include delayed motor milestones, difficult running or climbing stairs. Boys with DMD use the Gower´s maneuver to arise from floor. The majority of patients lost independent ambulation at around 12 years. Cardiomyopathy and respiratory failure most often occur in the third decade.

In addition to motor impairment due to myopathy, boys with DMD often have disorders of the central nervous system. Cognitive impairment and attention deficit disorders have been found in approximately one third of DMD boys, prevalence of autism in DMD patients varies from 5 to 15% in various studies [3,4]. Epilepsy has been reported in about 3-6% of DMD boys [5].

Case Report

A male child was born at full term to unrelated healthy parents. There was no history of any neuromuscular disorder in the family. The patient was admitted to hospitalization at the Department of Child Neurology at 8 months of age for suspicion of epileptic seizures. He underwent video-EEG, where epileptic spasms were recorded and vigabatrin was introduced leading to seizure freedom. Brain MRI with normal findings was performed. After 10 days of using vigabatrin patient cought a cold without fever. There was elevation of ALT (2.29 μkat/l), AST (5.22 μkat/l) as well as of CK (318.79 μkat/l) and myoglobin (854 μg/l) in laboratory tests and patient was transferred to the Metabolic centre in Prague with the diagnosis of West syndrome complicated with rhabdomyolysis during infection. There he underwent lot of testing, molecular genetics included. Because of suspicion of X-linked infantile spasms syndrome, analysis of CDKL5 and ARX gene was done with no mutation found.

During this hospitalization skin and muscle biopsies were also performed. A muscle biopsy revealed a myopathic pattern with dystrophic changes including fiber size variation, necrosis and regeneration (Figure 1). Focally, small collections of lymphocytes were observed in the endomysium. Immunohistochemically, all three dystrophin domains examined (C-terminus, N-terminus and rod domain) were completely missing and N-utrophin was upregulated on the surface of all muscle fibers (Figure 2). Focal deficits or weakening of the immunoreactions were observed also in case of sarcoglycans and dysferlin. Merosin and emerin were normally present. Based on that, dystrophinopathy was suspected.

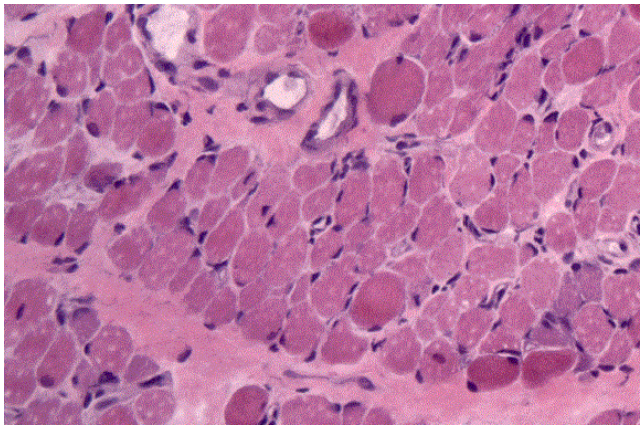

Figure 1: Muscle biopsy-myopathic pattern with dystrophic changes including fiber size variation, necrosis and regeneration (hematoxylin-eosin, original magnification 400X).

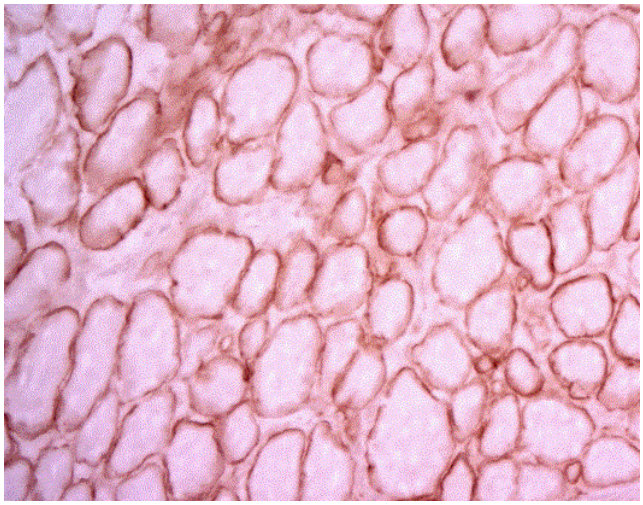

Figure 2: N-utrophin immunohistochemistry showing diffuse upregulation of the protein (original magnification 400X).

Following molecular genetic testing of the dystrophin-DMD gene (MLPA analysis), was performed with the result of the deletion of exons 10 and 11 in the DMD gene. The diagnosis of Duchenne muscular dystrophy was therefore confirmed. Our patient is still clinically presymptomatic with normal walking, no cardiomyopathy, no respiratory problems; he has only mild calf pseudohypertrophy without contractures of the Achilles tendons.

Unfortunately, at the age of 2 years epileptic seizures reoccurred. The patient had focal seizures with evolution to secondary generalization. Levetiracetam was introduced without any effect. At that time he had 12 seizures per day. Antiepileptic treatment was introduced parenterally–clonazepam and phenobarbital with partial effect. Because of myorelaxing effect of clonazepan and his insufficient antiepileptic effect, we tapered it off. Topiramate was started and the combination of vigabatrin, phenobarbital and topiramate led to seizure freedom lasting for 3 years. Finally, this three–combination of antiepileptic drugs seems to be effective in an epileptic seizure control.

Psychological examination

During hospitalizations we observed that patient's mental and speech development was delayed and we also realized an atypical social contact (especially lack of eye contact).

He was examined by paediatric psychologist with conclusion of low functioning child autism with severe symptoms of the triad; passive social type and severe mental retardation with typical cognitive profile (higher scores on measures of visual-spatial ability with very poorly developed verbal comprehension). A significant impairment of social reciprocity was described. He did not make any social approach and did not show any normal patterns of social responsiveness (e.g., eye contact, social smile). Relationship with his parents lacked warmth and he was not interested in other children or their play. His ability of expressive language was impaired, comprising of repetitive syllables with no communication purpose, used during spontaneous activity only. No compensative nonverbal communication was seen. Comprehension was limited to few basic instructions. His range of interest was restricted, consisting mainly of repetitive stereotyped behavior (e.g., rummaged in little cubes) and wasn't interested in any toys or engaged in pretend play.

Discussion

We present a 4 year-old boy with a combination of an inherited neuromuscular disorder – Duchenne muscular dystrophy, autism and epilepsy. The reported prevalence of DMD/BMD is 1 in 3500 live male births [2]. The prevalence of pervasive developmental disorder is estimated at about 0.62-0.70%, with autism being about 4 times more prevalent in males than in females [6]. An association between Duchenne muscular dystrophy and autism spectrum disorders has already been described. Wu et al. in his study found that in 158 patients with DMD there were 6 with autism spectrum disorder [1]. Darke et al. reported 5.4% of the Duchenne males in their study having a pre-existing autism spectrum disorder [7]. Banihani et al had 59 DMD boys in their retrospective study. Full scale IQ of less than 70 was seen in 27%, learning disability in 44%, intellectual disability in 19%, attention-deficit/hyperactivity disorder in 32% and autism spectrum disorders in 15% [3]. They confirm hypothesis that there could be association between Duchenne muscular dystrophy and autism spectrum disorder as they co-occur more often than expected by chance. The association of DMD with central nervous system disorders or autism spectrum disorder suggests several different possible mechanisms of action. The brain has one of the highest levels of the dystrophin expression, second only to muscles.

Seizures are very common in children with autism. Francis et al. states that lifetime incidence of epilepsy in autism varies from 5 to 46% in various studies [8].

The prevalence of epileptic seizures in DMD patients is about 3-6%, also higher than in the general pediatric population (0.5-1%). It was seen more often in patients with mutations between exon 31 and 62 (7.5%), less in patients with mutations upstream exon 31(3.7%) [9,10]. The DMD gene produces a range of different transcripts encoding various dystrophin isoforms, i.e. proteins of varying lengths containing different segments of the basic dystrophin sequence [11]. These isoforms are encoded by a range of different mRNA's which are generated by several processes, mainly the use of different, unique and

often tissue-specific promoters, alternative splicing, and different signalling pathways. The isoform Dp427c is expressed predominantly in neurons of the cortex and the hippocampus. The Dp427c isoform is also known as brain dystrophin [4,12].

Mechanism of association of DMD and epilepsy can be similar to association of DMD and autism spectrum disorders. The full-length dystrophin isoforms are found in the cortex, hippocampus and cerebellum. The shorter isoforms are expressed in glia. A loss of these isoforms (particularly Dp71) causes a major alternation in the levels of aquaporin-4 which is implicated in neuronal hyperexcitability and in the genesis of seizures [10]. These findings could help to elucidate the pathophysiology of epilepsy in dystrophinopathies.

Our patient presented with the deletion of exons 10 and 11 of the DMD gene, however it is still unclear, whether deletions of specific exons are more or less associated with the central nervous system impairment.

To the best of our knowledge, this unusual phenotype, consisting of DMD, epilepsy, and autism, has not been reported as yet. We postulate, that this "triple trouble" is not just a coincidence, but more likely a result of the same underlying pathophysiological process – the dystrophin deficiency.

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