Abstract:
Duchenne muscular dystrophy is an X-linked recessive disease due to mutation in dystrophin gene. A significant proportion of children with DMD suffer from mental retardation, cognitive impairment and psychiatric symptoms. Although there are many researches about mental retardation as one of the CNS complications in DMD, there are few reports on epilepsy in this disease. A 14 years old boy who had genetically proven Duchenne muscular dystrophy presented with intractable complex partial seizures. He had normal psychomotor development. He developed progressive weakness of limbs since 5 years of age and became wheelchair bound since 10 years of age. He had recurrent episodes of sudden vacant stare with forced deviation of head and eyes to right side followed by facial twitching on the right side and involuntary micturition. Each episode lasted for about 10 to 15 minutes occurring atleast once or twice a month for past 6 years. He is on carbamazepine at 20mgkg and levetiracetam at 37mgkg with good compliance. Molecular analysis revealed exon 17 deletion of dystrophin gene. He had elevated serum CPK and RBBB in ECG. Echo revealed dilated cardiomyopathy. MRI brain was normal. EEG revealed bursts of bilateral spike and wave discharges. Thus, epilepsy may be a rare associated feature of DMD. Absence of dystrophin in the central nervous system causing suppression of inhibitory synapses in cortex and hippocampus may be the pathogenesis of epilepsy in this disease.

Keyword: Epilepsy, Duchenne Muscular Dystrophy (DMD), Dystrophin

INTRODUCTION:
Muscular dystrophies are progressive, inherited skeletal muscle disorders resulting in muscle degeneration and loss of strength. Dystrophinopathies are a group of muscular dystrophies resulting from mutations in the dystrophin gene, located in the Xp21 region. Of these, Duchenne muscular dystrophy (DMD) is the most common dystrophinopathy, resulting from complete absence of the dystrophin gene product: the subsarcolemmal protein, dystrophin. The dystrophin is expressed not only in skeletal muscle but also in kidney, heart, retina as well as central nervous system.
35% of patients with DMD have mental retardation, cognitive dysfunction and neuropsychiatric manifestations. Although there are many studies regarding the cognitive impairment as CNS complication of DMD, there are very few reports regarding the occurrence of epilepsy in this disease. We report a case of genetically proven duchenne muscular dystrophy with a rare coexistence of partial epilepsy with secondary generalisation. CASE VIGNETTE A 14 years old boy first born out of non-consanguinous marriage with normal perinatal period and psychomotor development, presented with progressive difficulty in walking and getting up from up lying down and squatting posture since 5 years of age. He became wheel chair bound since 10 years of age. Since 8 years of age, patient had been getting recurrent episodes of complex partial seizures with the semiology being sudden unresponsiveness with vacant stare followed by facial twitching on the right side associated with involuntary micturition. Each episode lasts for about 5 to 10 minutes and stops spontaneously. There is postictal drowsiness for about half an hour. He was getting episodes of seizures once in 7 – 10 days. Patient was treated with Tab. Sodium valproate 200mg thrice daily. The seizures were not controlled and then he was started on Tab.Levetiracetam 500mg twice daily. For past 1 year, the seizure frequency has been reduced to once a month. There are no similar complaints or any other neurological illness among the siblings or the other family members. On examination, patient had normal higher mental functions and cranial nerve functions. He had pseudo hypertrophy of both calf muscles and bilaterally symmetrical proximal weakness of both lower limbs. (Power - 2/5 in both lower limbs). Deep tendon reflexes were normally elicitable and bilateral flexor plantar. Investigations revealed elevated serum CPK and echocardiogram showed dilated cardiomypathy with RBBB in ECG. Molecular analysis revealed exon 19 deletion of Dystrophin gene. EEG showed normal background rhythm with bursts of generalised spike and wave discharges suggestive of epileptiform activity. MRI brain and spine were normal.

DISCUSSION: Duchenne muscular dystrophy (DMD) is a hereditary, X-linked, progressive muscular disorder characterized by progressive weakness of skeletal muscles and respiratory and cardiac impairment, caused by mutations in the dystrophin gene. Cognitive impairment and attention deficit disorders have been found in approximately a third of DMD boys and are generally associated with mutations those after exon 31 and more consistently with mutations after exon 63, i.e. the mutations affecting the shorter isoforms expressed in the brain. Epilepsy, in contrast, has been reported in about 3% of DMD boys. DMD is the result of a mutation in dystrophin gene and dystrophin is a membranous protein located in the inner surface of plasmalema. Other than its known role in skeletal muscle, it’s role in some other tissues such as cortex, hippocampus and cerebellum has also been described which has co-localization with GABA-A receptor in some inhibitory synapses. Knuesel et al (1999) found co-localisation of GABA A channel with dystrophin in mouse cerebellum and hippocampus. In the cerebral cortex, the dystrophin clusters and GABA A clusters were found separately as well as groups of dystrophin and GABA A clusters together, indicating a possibility of GABA A subset dependent co-localization of dystrophin. It has been speculated that a possible role of dystrophin in the brain is anchoring or

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clustering and stabilization of GABA-A receptors. 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. GABA receptor is one of inhibitory receptors of brain and the suggestion that reduction in GABAergic inhibition causes acute seizure has been proposed. This idea originates from the known role of GABA-mediated inhibitory drugs in controlling epilepsy. According to prior discussed impressions, we can hypothesize that reduction in GABA-A receptors in Duchenne muscular dystrophy may eliminate its inhibitory role on epileptic discharges and this in turn would result in increasing the risk of epilepsy in these patients. Dystrophin has been found to have a structural role in maintaining integrity of lipid bilayer when it undergoes mechanical and osmotic stresses, and so in the absence of dystrophin the membrane ruptures and allows influx of extracellular ions, calcium causing disturbances in regulating oxidative metabolism in hypoxic situations and the absence of dystrophin also results in glucose hypometabolism. There is much evidence that GABA-A receptor potentiates tolerance to hypoxic situations. 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. 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. There are some evidences at molecular level substantiating the cognitive impairment and low IQ in patients with DMD are present. Rapaport et al (1991) found that 70% of patients with deletion in exon 52 have cognitive impairment. Most recently, an association between the degree of cognitive impairment and the presence of mutation in the Dp71 isoform of dystrophin gene has been reported. (Moizard et al 2000). Epilepsy with generalized tonic-clonic seizures in 3 boys and infantile spasms in another boy of 201 boys with Duchenne dystrophy and generalized tonic-clonic seizures in 3 boys and absence and generalized tonic-clonic seizures in another boy of 53 boys with Becker dystrophy have been reported by Gudwin et al (1997). There are several dystrophin isoforms that show a tissue specific pattern of expression. These include a) the muscle, brain and Purkinje cell isoforms, expressed predominantly in skeletal and cardiac muscle and the central nervous system (CNS); b) Dp260 predominantly expressed in the retina; c) Dp140 thus far detected in the CNS and kidney; d) Dp116 expressed in the peripheral nerve; e) Dp71 expressed in a variety of non-muscle tissues, including brain; f) Dp40, with a similar distribution to that of Dp71 but only during early development. As suggested by few animal studies, all the dystrophin isoforms appear to have a possible role in epileptogenesis with a number of mechanisms related to their different regional and subcellular distribution in the brain. The full-length isoforms localize to a subset of GABAergic synapses in the cortex, hippocampus, and cerebellum. The shorter isoforms, in contrast, are expressed in glia. A loss of these isoforms (particularly Dp71) causes a major alteration in the levels of aquaporin-4 (AQP4), which is implicated in neuronal hyperexcitability and in the genesis of seizures.
Dp71 is the most abundant dystrophin in brain and liver and the predominant isoform in astrocyte and glioma cell cultures. The Dp71 isoform is also known as apo-dystrophin-1. Gheorghe Benga et al.,(2006) has reported a decreased water permeability of RBC in patients with Duchenne muscular dystrophy. These findings were interpreted as an expression of generalized membrane defects affecting water permeability in epilepsy and Duchenne muscular dystrophy. In recent years this idea was confirmed by reports indicating aquaporin abnormalities in the brain of epileptic patients and in the muscle of Duchenne muscular dystrophy patients. Aquaporins are specialised water channels in the plasma membranes of some cells that permit water to be transported through the lipid bilayer much more efficiently than by simple diffusion. The critical biologically active transporters was called “Aquaporins”(Aqp) by Peter Agre nobel prize winner. The most abundant Aquaporin in brain is Aqp 4 which is crucial for brain water and ion homeostasis during rapid neural activity. These aquaporin4 are found in dystrophin – protein complex. The reduction in dystrophin-protein complex leads to mislocalization of Aqp 4 in astrocytes resulting in loss of ion and water homeostasis that contributes to epileptogenesis16.

CONCLUSION: The various hypotheses regarding susceptibility of epilepsy in patients with DMD favour the importance of considering epilepsy, though rare, as yet another CNS complication of DMD apart from cognitive impairment. Further investigations and research with larger sample size and more meticulous focus on the background of epilepsy in patients with DMD are suggested to target an appropriate treatment of the complications that can be treated in an otherwise progressive illness.


13 Goodwin F, Muntoni F, Dubowitz V:

