



Epilepsy in Duchenne and Becker muscular dystrophies

FIONA GOODWIN, FRANCESCO MUNTONI, VICTOR DUBOWITZ

Neuromuscular Unit, Department of Paediatric and Neonatal Medicine, Hammersmith Hospital, London, UK

Duchenne and Becker muscular dystrophies are X-linked allelic disorders in which the association of central nervous system dysfunction, typically in the form of mental retardation, is a well recognized feature. They are both due to mutations in the dystrophin gene, whose corresponding protein products are expressed both in the muscle and central nervous system. We have observed an increased frequency of epilepsy in children with Duchenne and Becker muscular dystrophy attending our clinic. Out of 254 boys with this condition (201 Duchenne and 53 Becker), eight children, four in the Duchenne and four in the Becker group, had a confirmed diagnosis of epilepsy (cumulative incidence 3.14%, with a subgroup incidence of 1.99% in the Duchenne and 7.54% in the Becker group). Statistical analysis indicated that only the incidence of epilepsy in Becker muscular dystrophy was significant ($p < 0.007$). Our data suggests that epilepsy may be a rare associated feature in children with muscular dystrophy secondary to dystrophin deficiency.

Keywords: Epilepsy. Duchenne muscular dystrophy. Becker muscular dystrophy.

Introduction

Duchenne and Becker muscular dystrophies (DMD and BMD) are allelic disorders due to mutations in the X-linked dystrophin gene. Mutations that result in severe disruption of the function of this gene give rise to DMD; no dystrophin is usually visible in the muscle biopsies of these children.^{1,2} Individuals with the milder BMD variant usually carry mutations that are compatible with the residual expression of dystrophin, which may be reduced in size and/or quantity.^{3–6} A significant proportion (approximately 35%) of children with DMD suffer from non-progressive mental retardation; cognitive impairment and psychiatric symptoms have also been reported in BMD, although their incidence is lower.^{7–10}

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 (see refs 11 and 12 for a review).

The relation of dystrophin mutations and cognitive impairment is not clear. It has, however, been reported that deletions affecting the distal portion of the gene are more likely to be associated with mental retardation.^{13,14} Behavioural abnormalities have also been documented in the *mdx* mouse, an animal model for DMD, further suggesting a link between lack of dystrophin and CNS dysfunction.¹⁵

We reviewed the data of 201 DMD and 53 BMD children currently attending the Hammersmith

Received 24.4.97. Revised 23.7.97. Accepted 18.8.97.

Correspondence: Dr Francesco Muntoni, Department of Paediatric and Neonatal Medicine, Hammersmith Hospital, London, Du Cane Road, London W12 0NN, UK

Hospital. Eight children (four DMD and four BMD) had a confirmed diagnosis of epilepsy, a prevalence of 3.1% in this cohort of 254 children (1.99% in the Duchenne and 7.54% in the Becker group). As the prevalence of epilepsy in the general paediatric population is reported as 0.4–0.5%,^{16,17} our data suggest that there could be an association between epilepsy and dystrophinopathies.

Clinical cases

Case 1: Duchenne dystrophy and generalized tonic–clonic seizures

A diagnosis of DMD in this boy was made at birth following the finding of elevated serum creatine kinase (CK) (there was a positive family history). His condition followed a typical course and he became wheelchair bound at the age of 12 years. Muscle biopsy showed absent dystrophin and genetic studies failed to identify a deletion. He attended a normal school. He had his first generalized tonic–clonic seizure at the age of 3 years and continued to have several fits a month. He was started on sodium valproate at the age of 5 years with excellent control of seizure frequency. He stopped taking the medication when he was 12 years old because he had been seizure free for more than 2 years. Generalized tonic–clonic seizures recurred within 9 months and he was restarted on medication. His cousin, also affected by DMD, did not suffer from epilepsy.

Case 2: Duchenne dystrophy and generalized tonic–clonic seizures

This boy became symptomatic at the age of 4 years and eventually lost ambulation aged 12 years. A deletion of exons 45–51 was found. He is in the lower range of normal intelligence, as defined by school performance. He had his first generalized tonic–clonic seizures at the age of 11 years. An EEG showed high voltage delta components at 3Hz evident over the posterior regions with a right-sided predominance. Overbreathing caused generalization of these abnormalities, while photic stimulation at a frequency of 15–18Hz elicited bursts of spikes and polyspikes and waves. Treatment with sodium valproate successfully decreased the frequency of his seizures. There was no family history of seizures or of DMD.

Case 3: Duchenne dystrophy and infantile spasms

This child presented at 10 months of age with infantile spasms. The electroencephalogram (EEG) was hypsarrythmic. Extensive investigations to exclude a metabolic disease, including brain magnetic resonance imaging (MRI), were normal. Adrenocorticotrophic hormone treatment caused a complete cessation of the infantile spasms within 3 days. By 15 months, however, he was noted to have significant global developmental delay, as he was not sitting or saying any words. He could walk independently at the age of 3 years and began to say single words at 3½ years. Currently, aged 4½ years, he only says three words, has an autistic behaviour, cannot run properly and has a minimal Gowers' manoeuvre. A repeated EEG at the age of 3 years did not show any epileptiform activity, but only a slowing of the background. His serum CK levels were incidentally found to be elevated at the age of 15 months. A muscle biopsy showed absent dystrophin staining with N terminal and mid-rod antibodies (Dys 1 and 3) but positive with C terminal antibodies (Dys 2). A large in-frame deletion (exons 13–40, 3' end-point not defined) was found. Considering both the current functional abilities of this child and the fact that patients reported so far with such a large deletion in the 5' end of the dystrophin gene followed a severe disease course,¹⁸ we would anticipate a DMD phenotype in this boy. There was no family history of seizure or of DMD.

Case 4: Duchenne dystrophy and generalized tonic-clonic seizures

A diagnosis of DMD was made in this boy, with an older affected brother, soon after birth because of elevation of serum CK. He remained ambulant until the age of 10 years, and was of normal intelligence. He had a generalized tonic–clonic seizure at the age of 14 years whilst playing on his computer. An EEG was abnormal with bursts of paroxysmal slow-wave activity and generalized epileptiform activity elicited by photic stimulation. He was not started on medication because he had no further seizures until the late teens, when he developed generalized tonic–clonic seizures again. He was then treated with sodium valproate with no further seizure recurrence. Deletion data were not available in this case. His affected brother did not develop epilepsy. No other member of his family was affected by DMD or seizures.

Case 5: Becker dystrophy and generalized tonic-clonic seizures

This 9-year-old boy presented at 4 years with cramps and frequent falls. A needle muscle biopsy and genetic studies (deletion of exons 45–47) confirmed the clinical diagnosis of Becker muscular dystrophy. He currently is able to run, hop and rise fairly easily from the floor. He is of normal intelligence and is doing well in mainstream school. He had his first fit, a generalized tonic-clonic seizure, at the age of 8 years. Three months later he had two further generalized tonic-clonic seizures during the night, after which he was started on carbamazepine. He had five further fits in the following year. An EEG recorded after the first fit showed non-specific bilateral abnormalities without any focal features. There was no family history of seizures or muscular dystrophy.

Case 6: Becker dystrophy and generalized tonic-clonic seizures

This boy was referred at the age of 12 years, being clumsy and already having a diagnosis of epilepsy. A needle muscle biopsy and genetic studies (deletion of exons 10–30) confirmed the clinical diagnosis of Becker muscular dystrophy. He had progressive weakness and lost mobility at the age of 23 years. His fits began at the age of 9 months as tonic seizures and later on progressed to generalized tonic-clonic seizures occurring mostly during the day, occasionally at night. He was treated initially with phenobarbitone and later with phenytoin, which improved but did not completely control his seizures. An EEG at the age of 14 years showed spikes in the right parieto-temporal area. Behavioural problems and poor control of his epilepsy created significant educational difficulties. There was no family history of seizures or BMD.

Case 7: Becker dystrophy with absences and generalized tonic-clonic seizures

This 14-year-old boy has mild BMD and is able to run, jump and has a minimal Gowers' manoeuvre. He suffers from a contiguous gene syndrome affecting, in addition to dystrophin, also the genes responsible for glycerol kinase deficiency and congenital adrenal hypoplasia. He also had bilateral undescended testes and mild mental retardation. At the age of 8 years he developed infrequent generalized tonic-clonic seizures during sleep. A few years later he developed typical

absences and an EEG showed a burst of spike-wave activity at 3 Hz. Hyperventilation induced exacerbation of these EEG changes. He responded very well to sodium valproate. He has two younger brothers, similarly affected, but they have not developed epilepsy. The deletion present in this family is likely to affect the 3' untranslated region of dystrophin as we were able to show a faint staining with the C-terminal anti-dystrophin monoclonal antibody Dys 2, raised against the last 17 amino acids of the molecule.

Case 8: Becker dystrophy with generalized tonic-clonic seizures

This child was referred to us at the age of 6 years, because of difficulties in running and cramps on exercise. A clinical diagnosis of BMD was confirmed by the finding of abnormal dystrophin staining in his muscle biopsy and a deletion of exons 45–49. Currently, at the age of 9 years, he is able to run, hop and jump, and has no Gowers' signs. He has dyslexia. Recently he had a prolonged episode of generalized tonic-clonic seizures. An EEG showed a normal background activity, but frequent symmetrical, raised voltage, rhythmical slowing at 3–7 Hz with sharp morphology, more evident over the right hemisphere, and hyperventilation induced an exacerbation of these paroxysmal slow waves with associated spikes over both hemispheres. He had several further generalized tonic-clonic seizures and increased generalized bursts of spike and wave paroxysms after starting carbamazepine treatment, that was immediately discontinued. The child was then started on valproate therapy with excellent control of seizures. There was no family history of BMD; a maternal cousin, however, is also affected by epilepsy (generalized tonic-clonic seizures).

Statistical analysis

The overall prevalence of epilepsy in our population of DMD and BMD was 3.14%. Statistical analysis suggested that this number is significantly different from the 0.5% expected for an age-matched population ($p < 0.01$, Fisher's exact test). Analysis of the DMD and BMD separately suggested a higher prevalence of epilepsy in BMD (7.54%, $p < 0.007$, Fisher's exact test). The epilepsy prevalence in DMD was also higher than expected (1.9%) but the difference was not statistically significant.

Discussion

In this report we describe an increased prevalence of epilepsy in patients with DMD and BMD, an association which has not been documented previously. Our statistical analysis suggests that the prevalence of epilepsy is significantly higher only in BMD children. Seven of the eight boys described (all BMD and three DMD) had generalized tonic-clonic seizures (in one BMD absence seizures co-existed). In two of the DMD, photic stimulation elicited generalized epileptiform activity. A child with DMD and severe mental retardation had idiopathic infantile spasms. The significance of the co-occurrence of muscular dystrophy and infantile spasms in this child is not very clear, and an increased incidence of epilepsy, including infantile spasms, is a recognized feature of children with mental handicap. Mild mental retardation was also a feature of two of the four BMD children; the other five children, however, had normal intellect.

Although this is not an epidemiological study and a bias of ascertainment might have affected our results, only two of these children developed epilepsy prior to their referral to us for the management of their muscular dystrophy. Seizures were under good pharmacological control in one of these two children, so that it is unlikely that the reason for their referral was related to the epilepsy.

Previously, EEG abnormalities (but not seizures) have been described in boys with DMD, with frequencies varying between 56% and 82%.^{9,10} When EEG abnormalities were correlated with IQ in two studies, a higher frequency of abnormalities in the lower IQ group was found by some authors¹⁰ but not others.⁹ A high incidence of focal abnormalities (82.7%) was also found.¹⁰ In addition, Nakao *et al.*¹⁹ reported that 29% of EEGs in female carriers were abnormal and there is a case report of a female Duchenne patient with Turner's syndrome who also had epilepsy.²⁰

The reason for an apparent increased prevalence of epilepsy in our children with a dystrophinopathy is not known. Various dystrophin isoforms are expressed in the central nervous system in addition to muscle.^{11,12} However, we did not identify any single unifying mutation in our cases of children with epilepsy. It is possible that abnormal neuronal excitability is a result of altered expression of dystrophin in the central nervous system and abnormal retinal neuronal excitability has been demonstrated in DMD *in vivo*.²¹ Another possibility is that neuronal migration defects may exist in patients with DMD or BMD. Such

abnormalities have been found in the brain of children with DMD in some studies²² but have not been confirmed in others.²³ None of our patients had a focal epilepsy, making this latter hypothesis less attractive.

Whatever the mechanism accounting for an increased prevalence of epilepsy in these children might be, the discordance between the muscular dystrophy and the presence of epilepsy in the three cases with a positive family history (cases 1, 4, 7), suggests that its action is probably that of lowering the seizure threshold in children with a dystrophinopathy.

Formal epidemiological studies are needed to confirm our hypothesis that epilepsy may be another manifestation of abnormal expression of dystrophin in the CNS.

Acknowledgements

Dr F Goodwin was a Trainee Fellow supported by the Muscular Dystrophy Group of Great Britain and Northern Ireland. We wish to thank Dr CA Sewry, London, for performing the histopathology and immunocytochemistry on the muscle biopsies. We also wish to thank Dr S Abbs and R Roberts, London, for performing the DNA deletion screening and Dr R Newton, Chertsey, for providing clinical information on one child.

References

- 1 Koenig M, Hoffman EP, Bertelson CJ *et al.* Complete cloning of the Duchenne muscular dystrophy cDNA and preliminary genomic organisation of the DMD gene in normal and affected individuals. *Cell* 1987; 50: 509-517.
- 2 Hoffman EP, Brown RH, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell* 1987; 51: 919-928.
- 3 Chelly J, Gilgenkrantz H, Lambert M *et al.* Effect of dystrophin gene deletions on mRNA levels and processing in Duchenne and Becker muscular dystrophy. *Cell* 1990; 63: 239-248.
- 4 Hoffman EP, Fischbeck KH, Brown RH *et al.* Characterization of dystrophin in muscle biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. *New Engl J Med* 1988; 318: 1363-1368.
- 5 Koenig M, Beggs AH, Moyer M *et al.* The molecular basis for Duchenne versus Becker muscular dystrophy: correlation of severity with type of deletion. *Am J Hum Genet* 1989; 45: 498-506.
- 6 Monaco AP, Bertelson CJ, Liechti-Gallati S *et al.* An explanation for the phenotypic differences between

- patients bearing partial deletions of the DMD locus. *Genomics* 1988; 2: 90–95.
- 7 Dubowitz V. Intellectual impairment in muscular dystrophy. *Arch Dis Child* 1965; 40: 296–301.
 - 8 Leibowitz D, Dubowitz V. Intellect and behaviour in Duchenne muscular dystrophy. *Develop Med Child Neurol* 1981; 23: 577–590.
 - 9 Florek M and Karolak S. Intelligence level of patients with Duchenne type of progressive muscular dystrophy. *Eur J Pediatr* 1977; 126: 275–282.
 - 10 Kozicka A, Prot J, Wasilewska R. Mental retardation in patients with Duchenne muscular dystrophy. *J Neurol. Sci.* 1971; 14: 209–213.
 - 11 Ahn AH, Kunkel LM. The structural and functional diversity of dystrophin. *Nat Genet* 1993; 3: 283–91.
 - 12 den Dunnen J, Bakker BE. Duchenne/Becker muscular dystrophy data pages. The World Wide Web: <http://ruly70.medfac.leidenuniv.nl/~duchenne/#-diagtech>.
 - 13 Hogdson S, Abbs S, Clerk S *et al.* Correlation of clinical and deletion data in Duchenne and Becker muscular dystrophy, with special reference to mental ability. *Neuromusc Disord* 1992; 2: 269–276.
 - 14 Lenk U, Hanke R, Thiele H, Speer A. Point mutations at the carboxy terminus of the human dystrophin gene: implications for an association with mental retardation in DMD patients. *Hum Mol Gen* 1993; 2: 1877–1881.
 - 15 Muntoni F, Mateddu A, Serra G. Passive avoidance behaviour deficit in the mdx mouse. *Neuromusc Disord* 1991; 1: 121–123.
 - 16 Cowan L *et al.* Prevalence of the epilepsies in children and adolescents. *Epilepsia* 1989; 30: 94–106.
 - 17 Ross EM, Peckham CS. Seizure disorders in the national child development study. *Research Progress in Epilepsy*. London: Pitman, 1989: 46–59.
 - 18 Winnard AV, Klein CJ, Coover DD *et al.* Characterization of translational frame exception patients in Duchenne/Becker muscular dystrophy. *Hum Mol Genet* 1993; 2: 737–744.
 - 19 Nakao K, Kito S, Muro T *et al.* Nervous system involvement in progressive muscular dystrophy. *Neurol Proc Aust Assoc* 1968; 5: 557–564.
 - 20 Bjerglund-Nielsen L, Nielsen IM. Turner syndrome and Duchenne muscular dystrophy in a girl with an X autosome translocation. *Ann Genet* 1984; 27: 173–177.
 - 21 De Souza VN, Nguyen TM, Morris GE *et al.* A novel dystrophin isoform is required for normal retinal electrophysiology. *Hum Mol Genet* 1995; 4: 837–842.
 - 22 Jagadha V, Becker LE. Brain morphology in Duchenne muscular dystrophy: a golgi study. *Pediatr Neurol* 1988; 4: 87–92.
 - 23 Dubowitz V, Crome L. The central nervous system in Duchenne muscular dystrophy. *Brain* 1969; 92: 805–808.