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REVIEW ARTICLE

Brain function in Duchenne muscular dystrophy

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Summary

Duchenne muscular dystrophy (DMD) is the second most commonly occurring genetically inherited disease in humans. It is an X-linked condition that affects approximately one in 3300 live male births. It is caused by the absence or disruption of the protein dystrophin, which is found in a variety of tissues, most notably skeletal muscle and neurones in particular regions of the CNS. Clinically DMD is characterized by a severe pathology of the skeletal musculature that results in the premature death of the individual. An important aspect of DMD that has received less attention is the role played by the absence or disruption of dystrophin on CNS function. In this review we concentrate on insights into this role gained from investigation of boys with DMD and the genetically most relevant animal model of DMD, the dystrophin-deficient *mdx* mouse. Behavioural studies have shown that DMD boys have a cognitive impairment and a lower IQ (average 85), whilst the *mdx* mice display an impairment in passive avoidance reflex and in short-term memory. In DMD boys, there is evidence of disordered CNS architecture, abnormalities in dendrites and loss of neurones, all associated with neurones that normally express dystrophin. In the *mdx* mouse, there have been reports of a 50% decrease in neurone number and neural shrinkage in regions of the cerebral cortex and brainstem. Histological evidence shows that the density of $GABA_A$ channel clusters is reduced in *mdx* Purkinje cells and hippocampal CA1 neurones. At the biochemical level, in DMD boys the bioenergetics of the CNS is abnormal and there is an increase in the levels of choline-containing compounds, indicative of CNS pathology. The *mdx* mice also display abnormal bioenergetics, with an increased level of inorganic phosphate and increased levels of choline-containing compounds. Functionally, DMD boys have EEG abnormalities and there is some preliminary evidence that synaptic function is affected adversely by the absence of dystrophin. Electrophysiological studies of *mdx* mice have shown that hippocampal neurones have an increased susceptibility to hypoxia. These recent findings on the role of dystrophin in the CNS have implications for the clinical management of boys with DMD.

Keywords: dystrophin; CNS; *mdx*

Abbreviation: DMD = Duchenne muscular dystrophy

Introduction

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 (Emery, 1991). In boys the disease presents as muscle weakness that is first apparent at 3–4 years of age. The muscle weakness is due to an irreversible, ongoing loss of skeletal muscle, and results in the need for a wheelchair at ~10 years of age and death at ~20 years, normally due to cardiorespiratory complications. The disease is a consequence of a mutation of the dystrophin gene, which comprises nearly 0.1% of the entire human genome (Koenig *et al*., 1987). The dystrophin gene has a high mutation rate, with approximately one-third of all new cases of DMD resulting from a spontaneous mutation (Barbujani *et al*., 1990). The product of the dystrophin gene was identified in the first successful application of the reverse genetics technique by both Kunkle (Kunkle *et al*., 1985) and Worton (Ray *et al*., 1985). Since the identification of the dystrophin protein and its location close to the inner surface of the plasmalemma there has been a substantial research effort aimed at investigating its physio-

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logical role in the cell membrane. These studies have mainly focused on skeletal muscle pathophysiology present in DMD and in animal models where dystrophin is known to be absent or present in a non-functional form. This work has given rise to two major hypotheses of the functional role of dystrophin in skeletal muscle The first is a calcium hypothesis, where calcium homeostasis of the cell is disrupted (Wrogemann and Pena, 1976; Duncan, 1989; Head, 1993) resulting in an increase in intracellular calcium and cell necrosis. The second hypothesis suggests that dystrophin plays a structural role in maintaining the integrity of the lipid bilayer when it undergoes mechanical and osmotic stresses, and that in its absence the membrane ruptures allowing an influx of extracellular ions, in particular calcium (Roses *et al*., 1975; Roses and Appel, 1976; Head *et al*., 1992).

Many case reports of DMD have indicated a significant CNS involvement, along with the skeletal muscle pathology that is characteristic of DMD. Indeed, Duchenne in his initial description noted that some boys displayed cognitive impairment (Duchenne, 1868). It is now well established that dystrophin is present in many cells throughout the body, including neurones of the CNS. In this review we will present recent evidence demonstrating that the absence or mutation of dystrophin in the CNS results in a significant disruption of neuronal and brain function. We will focus on work carried out in humans and in a dystrophin deficient murine model of DMD, the *mdx* mouse.

Evidence linking the absence of dystrophin with a cognitive impairment

In DMD boys

Since the original description of the disease by Duchenne (1868) in which he reported five patients with some degree of cognitive impairment, there has been debate as to whether there is in fact a cognitive deficit in the boys. This debate has been fuelled largely by conflicting reports about the prevalence of cognitive impairment in individual cases of boys with DMD. Gowers noted that 'in most recorded cases the mind has been unaffected' and concluded that intellectual impairment is not part of the disease (Gowers, 1879). Similar findings were reported by many investigators up until the 1970s (Morrow and Cohen, 1954; Walton and Natrass, 1954; Schoelly and Fraser, 1955; Truitt, 1955; Sherwin and McCully, 1961; Lincoln and Staples, 1977). However, there is now an overwhelming amount of evidence supporting Duchenne's original observation that in many cases there is a significant cognitive impairment. The average IQ of a boy with DMD is 85. The distribution of IQ in boys with DMD is shifted 1 SD lower, and consequently 30% of boys with DMD have an IQ of <70 (Allen and Rogkin, 1960; Worden and Vinos *et al*., 1962; Dubowitz, 1965, 1979; Zellweger and Niedermeyer, 1965; Zellweger and Hanson, 1967; Cohen *et al*., 1968; Prosser *et al*., 1969; Black, 1973; Marsh and Munsat, 1974; Florek and Karolak, 1977; Karagan and Zellweger, 1978; Karagan, 1979; Leibowitz and Dubowitz, 1981; Bresolin *et al*., 1994).

Although some earlier reports found a decrease in IQ in DMD boys compared with age-matched controls (Scheinfeld, 1950; Black, 1973; Florek and Karolak, 1977), the majority of studies, both longitudinal and correlational, found no such difference (Allen and Rodgin, 1960; Worden and Vignos, 1962; Zellweger and Niedermeyer, 1965; Zellweger and Hanson, 1967; Cohen *et al*., 1968; Prosser *et al*., 1969; Leibowitz and Dubowitz, 1981). Others have reported an increase in verbal IQ and a decrease in performance IQ with age, with full IQ remaining static (Prosser *et al*., 1969; Karagan and Zellweger, 1976; Sollee *et al*., 1985). Smith and colleagues reported that boys with DMD who were <6 years of age had a global developmental delay, particularly severe in language and locomotor areas, and showed a slight improvement with age (Smith *et al*., 1990). Deficits in verbal expression and in memory (Karagan *et al*., 1980), reading, mathematics and spelling (Dorman *et al*., 1988; Billard *et al*., 1998) and serial position memory (Anderson *et al*., 1988) have all been reported in DMD patients. Most recently Hinton and colleagues reported that regardless of IQ there was a specific cognitive profile, namely poor performance in digit span, story recall and comprehension, in a sample of 80 boys with DMD (Hinton *et al*., 2000). The authors note that, although there was a consistent profile of cognitive impairment, it was variable in degree, possibly due to the different dystrophin gene mutations in the boys sampled.

The search for a genotype/phenotype correlation for cognitive impairment in DMD has not led to any conclusive results. It has been considered that deletions more towards the 3′ end have a higher incidence of cognitive impairment (Bushby, 1992; Lenk *et al*., 1993). Rapaport found that 70% of patients with a deletion in exon 52 had cognitive impairment (Rapaport *et al*., 1991). Most recently, an association between the degree of cognitive impairment and the presence of mutation in the Dp71 isoform has been reported (Moizard *et al*., 2000). (For a complete account of the full-length dystrophin and the various isoforms, see Blake and Kröger, 2000; Mehler, 2000.)

In the mdx *mouse*

The *mdx* mouse is a murine model of DMD that lacks the full length dystrophin protein, but retains all the smaller dystrophin isoforms, including Dp71. Muntoni *et al*. (1991) were the first to report a cognitive deficit in the *mdx* mouse. Mice from 16–22 weeks old were found to have an impairment in passive avoidance learning. The cognitive impairment was further characterized by Vaillend and colleagues who found that *mdx* mice do not appear to have an impairment in task acquisition or in procedural memory, but rather they forget newly learned information more quickly than controls (Vaillend *et al*., 1995). Of interest is the finding that the *mdx* mouse, and the mdx^{3cv} mouse (which

lacks the full-length dystrophin as well as the smallest dystrophin isoform Dp71) are no different from controls in spatial discrimination tasks (Sesay *et al*., 1996; Vaillend *et al*., 1998). Although the evidence is not as strong as in DMD, it appears that in *mdx* mice the mutation of the full-length dystrophin protein is also correlated with a degree of cognitive impairment.

Histological evidence for a CNS deformity

In DMD boys

The results of brain autopsy, and more recently brain imaging, on DMD patients have not been consistent. Dubowitz and Crome investigated the brains on autopsy of 21 cases of classical DMD, and found only one case of abnormal brain weight and two cases where there were 'striking histological abnormalities' (Dubowitz and Crome, 1969). They concluded that DMD is not associated with any consistent gross or histological abnormality of the brain. Similarly, an MRI study by Bresolin and colleagues found no focal or generalized changes (Bresolin *et al*., 1994), but the sample was very small ($n = 4$). Rae and colleagues in a study of 15 DMD boys and 15 age-matched controls found no significant difference between these two groups in relative ventricular size, but stressed the young age (<13 years) of the boys in the sample (Rae *et al*., 1998*b*).

In contrast, other investigators have reported brain abnormalities in DMD patients ranging from slight to severe (Rosman and Kakulas, 1966; Rosman, 1970; Jagadha and Becker, 1988; Itoh *et al*., 1999). Among the abnormalities noted are neuronal loss, heterotopias, gliosis, neurofibrillary tangles, Purkinje cell loss, dendritic abnormalities (length, branching and intersections), disordered architecture, astrocytosis and perinuclear vacuolation. In 13 of 50 DMD patients studied, Bresolin and colleagues reported that the presence of macroglossia was significantly correlated with a low performance IQ (Bresolin *et al*., 1994). Schmidt *et al*. (1985), in agreement with Appleton *et al*. (1991), reported an increased head circumference in DMD patients, although these patients' fathers also showed greater head circumference as a group compared with normal. This was not the case in the mothers of these patients. They scanned (CT) three of the 36 subjects who were found to have a large head circumference and reported findings of 'probable megaencephaly'. The results of *in situ* brain measurements carried out on 30 DMD patients by Yoshioka *et al*. (1980) yielded more striking results. They found 67% of DMD patients studied had slight cortical atrophy, 60% had slight ventricular dilation and 30% had cortical atrophy, although clear signs of atrophy were only observed in older and more physically disabled patients (slight was defined as an enlargement of interhemispheric cisterns and sulci of 3–5 mm). Chen *et al*. (1999) reported a single DMD patient with mild brain atrophy, measured by CT scan.

There is some evidence to suggest that those DMD patients with identifiable brain abnormalities also show a cognitive impairment. Septien *et al*. (1991) studied 15 DMD patients, aged 4–16 years, in whom the average IQ was 84. In CT scans, 60% of the patients presented with slight cortical atrophy, with minimal dilation of the ventricles, interpreted as atrophy of the white matter. The nine cases presenting with cortical atrophy had an average IQ of 81, while the six presenting with normal CT scans had an average IQ of 90, although this difference was not statistically significant. In agreement with Yoshioka *et al*. (1980), they did find that cortical atrophy was more common in patients older than 10 years. In contrast, al-Qudah *et al*. (1990) found no correlation between MRI findings and verbal intelligence scores for four patients, two of whom were found to have mild atrophy consisting of dilation of lateral ventricles, CSF spaces and cerebral sulci. Overall these studies indicate that an abnormality of the brain, either gross or histological, is by no means common in DMD patients, and a correlation between abnormality and IQ impairment has yet to be clearly established. In those boys that do display abnormality in brain structure, the defects range from very mild to severe.

In the mdx *mouse*

In the original description of the *mdx* dystrophin deficient mouse, Bulfield *et al*. (1984) noted that the older (12 month old) mice displayed muscular tremors, possibly due to the older *mdx* mice having gross structural deformities in skeletal muscle, ranging from simple fibre splitting to complex multiple branching (Head *et al*., 1992). Interestingly, no gross abnormalities in brain or spinal cord were detected by Bulfield *et al*. (1984), or in a later study by Torres *et al*. (1987). In contrast, Sbriccoli *et al*. (1995) employed retrograde axonal tracing to study the structure of the corticospinal system in *mdx* mice, and reported substantial differences between the brains of *mdx* mice and controls. They found that the absolute number of cells was decreased by 50% in *mdx* mice compared with controls. The cell packing density of cortical layer 5 neurones was higher in *mdx* than controls, while the cell packing density of corticospinal neurones was lower in *mdx* than controls. Corticospinal cells constituted 50% of neurones present in layer 5 of controls, but only 35% in *mdx*. The authors concluded that rather than a shrinkage of all layer 5 cell populations, the origin of the corticospinal tract was selectively damaged, and thus there were fewer labelled neurones in *mdx* than controls. It is important to note that they found the number of spinal motoneurones was no different between *mdx* and controls. The cross-sectional area of labelled neurones was ~20% lower in *mdx* than controls, with the labelled cells also differing in shape (the *mdx* cells were rounder than the pyramidal-shaped control layer 5 cells). A more recent study by the same group (Carretta *et al*., 2001) investigated the organization of spinal projecting brainstem neurones. Cell counts of neurones were made in the red nucleus, the vestibular nuclear complex, the

medullary reticular formation and the raphe nuclei of *mdx* and control mice. Cell numbers in the red nucleus were less than half those of control mice, while numbers in the other brainstem structures remained largely unchanged. Interestingly, the red nucleus is the only group of brainstem neurones studied that is directly involved in the control of voluntary movements.

Recently, investigation of the structural abnormalities in the CNS has been extended to the receptor level. Knuesel *et al*. (1999) found co-localization of the $GABA_A$ channel with dystrophin in the mouse cerebellum and hippocampus. In *mdx* mouse cerebellum and hippocampus there was a marked reduction of $GABA_A$ clusters, but not in the striatum, which does not normally contain dystrophin. This decrease in clustering was noted to be particularly striking around the soma of cerebellar Purkinje cells. In both the cerebellum and hippocampus, the number (but not size) of $GABA_A$ clusters was reduced by ~50%. In the cerebral cortex, dystrophin clusters and $GABA_A$ clusters were observed separately, as well as groups of dystrophin and $GABA_A$ clusters together, indicating a possible $GABA_A$-subset-dependent co-localization of dystrophin (Knuesel *et al*., 1999).

Biochemical evidence for CNS involvement

In DMD boys

The search for the biochemical mechanisms underlying the mental deficit associated with lack of dystrophin has been necessarily limited. In 1994, Bresolin and colleagues published results from a PET study of fluorodeoxyglucose uptake showing decreased uptake in the cerebellum in DMD boys (Bresolin *et al*., 1994). This hypometabolism was shown not to occur in another subject of normal IQ with Wernig–Hoffman disease, suggesting that the cerebellar hypometabolism was unrelated to the motor deficit. Glucose hypometabolism is a common feature of disorders with associated cognitive deficits, and is generally indicative of lowered synaptic activity (Jueptner and Weiller, 1995). The mechanisms that give rise to the hypometabolism can be varied and diverse.

In 1995 a paper showing altered bioenergetics in DMD was published (Tracey *et al*., 1995). This study used neuropsychological testing and ^{31}P-magnetic resonance spectroscopy to examine the brains of 19 boys with DMD and 19 age-matched control boys. Results showed significantly higher ratios of inorganic phosphate compared with ATP, phosphomonoesters (mainly phosphocholine and phosphoethanolamine) and phosphocreatine. There was no significant correlation between these ratios and any measure of intellectual ability employed. Interestingly, the skeletal muscle of dystrophic boys has been shown to have a reduced total creatine and/or phosphocreatine concentration (Tarnopolsky and Parise, 1999). Patients with neuromuscular disorders such as DMD have been shown to be chronically hypercapnic (Misuri *et al*., 2000) due to the pattern of rapid, shallow breathing and one might expect this to have an effect on brain energetics.

Boys with DMD have also been shown to have elevated levels of choline-containing compounds (glycero- and phosphocholine) in certain regions of their brains. An autopsy study showed increased (up to three times higher) choline-containing compounds in the frontal cortex in boys older than 17 years (Kato *et al*., 1997), while a study using magnetic resonance spectroscopy *in vivo* showed significantly increased choline-containing compounds in the cerebellum, but not the cortex (Rae *et al*., 1998*b*), of boys younger than 13 years. The ratio of choline-containing compounds to *N*-acetylaspartyl-containing compounds was shown to correlate significantly with the boys' score on the Matrix Analogies Test, a measure of visuospatial cognitive ability that requires no verbal input and is tolerant of motor disability. As such, it is arguably a measure of DMD boys' underlying ability (i.e. taking verbal and motor deficits into account). This suggested that the increase in choline-containing compounds was possibly a 'compensatory' effect, although the authors pointed out that there was also a relationship between elevated choline-containing compounds and age, with the level of the compounds increasing with age. Choline-containing compounds are seen to be elevated in a number of brain disorders and are traditionally interpreted as symptomatic of increased membrane turnover or decreased membrane stability.

The cerebellar and hippocampal focus of the biochemical lesions in DMD are of interest due to the normally high expression of dystrophin in neurones found in these regions. Both Dorman *et al*. (1988) and Billard *et al*. (1998) noted that the reading deficits seen in those with DMD are similar to those seen in phonological dyslexia (Castles and Coltheart, 1993). Persons with phonological dyslexia, either developmental (Rae *et al*., 1998*c*; Nicolson *et al*., 1999) or acquired (Levisohn *et al*., 2000), have been shown to have abnormalities in the right cerebellum. Similarly, deficits in verbal working memory, a large component of the DMD cognitive deficit (Hinton *et al*., 2000) are known to have a cerebellar focus (Desmond *et al*., 1997).

In the mdx *mouse*

The accessibility of the *mdx* mouse model has meant that more invasive biochemical measurements have been possible. The bioenergetic abnormalities reported in DMD brain have also been documented in the *mdx* mouse, with an increased inorganic phosphate to phosphocreatine ratio and increased intracellular brain pH reported using ^{31}P-magnetic resonance spectroscopy *in vivo* (Tracey *et al*., 1996*a*). The mice studied were aged in the range 180–240 days. These authors also reported a reduction in total creatine content in aged *mdx* mice compared with controls which was not found in younger (60–150 days) mice (Tracey *et al*., 1996*b*). A similar reduction of creatine compounds is also reflected in muscle tissue of *mdx* mice (Pulido *et al*., 1998).

Metabolism of glucose is altered in the brains of mice which lack dystrophin. A recent study (Rae *et al*., 2001), using intravenous injection of [1-^{13}C]glucose and subsequent isotopomer analysis using NMR (nuclear magnetic resonance) spectroscopy, has shown significantly decreased free glucose in the brains of *mdx* mice compared with controls, but significantly increased fractional enrichment and increased flux of ^{13}C into metabolites such as glutamate and GABA, suggesting a faster metabolic rate in the dystrophin-deficient brain. Furthermore, muscimol, a $GABA_A$ (and partial $GABA_C$) agonist which normally induces sedation and decreases glucose use, has a decreased effect in *mdx* mice compared with controls. This suggests that the increased glucose use demonstrated in the *mdx* mouse brain may be due to decreased inhibitory input from the subset of abnormally clustered $GABA_A$ receptors.

Decreased bioenergetic buffering capacity would be expected to influence susceptibility to hypoxia. Mehler and coworkers have shown that hippocampal pyramidal neurones from *mdx* mice demonstrate increased sensitivity to hypoxia-induced loss of synaptic transmission (Mehler *et al*., 1992). A more recent study has shown more susceptibility of *mdx* hippocampal tissue slices to irreversible hypoxic failure compared with controls when kept in 10 mM glucose, but less susceptibility of *mdx* slices compared with controls when kept in 4 mM glucose (Godfraind *et al*., 2000). A substrate-dependent difference in oxygen consumption rates has also been demonstrated in *mdx* brain cortical tissue slices (Rae *et al*., 1998*a*, 2001), which consume oxygen at significantly higher rates than controls when metabolizing pyruvate at low oxygen partial pressures. In addition to decreased bioenergetic buffering capacity, the displayed altered response to hypoxia may also be influenced by the reported reduced $GABA_A$ receptor clustering in dystrophin-deficient mice (Knuesel *et al*., 1999), as $GABA_A$ receptor activation has been shown to exacerbate oxygen-glucose deprivation-induced neuronal injury (Muir *et al*., 1996).

A proton magnetic resonance study (Tracey *et al*., 1996*b*) reported normal levels of *N*-acetylaspartate, a neuronal viability marker (Bates *et al*., 1996), but increased whole-brain levels of choline-containing compounds (glycero- and phosphocholine) and *myo*-inositol. We have subsequently confirmed the increase in choline-containing compounds and localized them to the cerebellum and hippocampus (Rae *et al*., 2001).

An analysis of tissue from various organs in the *mdx* mouse, including the cerebellum, has shown that dystrophic tissue is easily distinguishable from control tissue based on its metabolic profile. Griffin *et al*. (2001) identify discernible metabolic changes in glycolysis, β-oxidation, the TCA cycle, the phosphocreatine/ATP cycle, lipid metabolism and osmoregulation. These were all in the five dystrophic tissues tested: cardiac muscle, diaphragm, skeletal muscle, cerebral cortex and cerebellum.

There is also some recent evidence suggesting that the water transporter aquaporin-4 is deficient in the astrocytic end feet in *mdx* mice (Frigeri *et al.*, 2001). Deficiency of the water transporter has also been reported in the muscle (Frigeri *et al.*, 2001) and erythrocyte membrane in DMD (Serbu *et al*., 1986). The deficiency in erythrocyte water transport is probably due to altered membrane fluidity in the erythrocyte (Ferretti *et al*., 1990), which does not normally express dystrophin. Altered expression of the dystrophin homologue β-spectrin has been reported, which is symptomatic of findings of altered expression of a range of proteins homologous to dystrophin in DMD, with no consistent pattern emerging (Boivin, 1992), although it has been suggested that it may result from genetic heterogeneity (Ashley and Goldstein, 1983).

Tracey *et al*. (1996*a*) reported increased extracellular and decreased intracellular volumes in *mdx* brain suggesting that the alteration in aquaporin-4 levels might result in alterations in the ability of cells in the brain to regulate cell volume. Although there has been one report of altered response to hypo-osmotic shock by *mdx* mouse muscle (Menke and Jockusch, 1991), recent work (Rae *et al*., 2001) has shown no difference in efflux rates of [^{3}H]taurine from *mdx* cortical brain tissue slices compared with controls when exposed to hypo-osmotic shock. The increase in total brain *myo*-inositol in *mdx* mice (Tracey *et al*., 1996*b*) might be interpreted as a response to chronic osmotic stress, as *myo*-inositol has been shown to act as an organic osmolyte in the brain (Strange *et al*., 1993).

Evidence from electrophysiological studies for an involvement of the CNS

In DMD boys

There have been very few electrophysiological studies carried out on DMD patients, due in large part to the practical and ethical problems associated with undertaking these types of measurements on sick boys. Overall the studies indicate a functional neural deficit in DMD. The majority of investigators, who have performed EEG studies on DMD patients, have found that a higher proportion (40–89%) of these patients display abnormalities compared with control groups or general age-matched population data (Wayne and Browne-Mayers, 1959; Perlstein *et al*., 1960; Zellweger and Niedermeyer, 1965; Nakao *et al*., 1968; Kozicka *et al*., 1971; Black, 1973; Florek and Karolak, 1977). The most consistent abnormality found was 14 and 6/s positive spikes, an abnormality also present in vegetative seizures, behavioural episodes, atypical seizures, migraines, autonomic nervous system dysfunctions, syncope and paroxysmal abdominal pain (Poser and Ziegler, 1958; Perlstein *et al*., 1960; Zellweger and Niedermeyer, 1965; Nakao *et al*., 1968). Unfortunately many of these studies lack appropriate control groups: Wayne and Browne-Mayers (1959), Perlstein *et al*. (1960), Zellweger and Niedermeyer (1965), Kozicka *et al*. (1971) and Florek and Karolak (1977) did not perform EEG studies on their own control groups. Barwick *et al*. (1965) did

use age-matched control boys and found abnormal or borderline recordings in 28% of DMD patients (n = 20) compared with 45% (n = 18) in the age-matched controls. Interestingly they did not observe any 14 and 6/s positive spikes. Zellweger and Niedermeyer (1965) suggest that this relatively low incidence of EEG abnormalities in DMD patients is due to small patient numbers and the criteria set for definition of positive spike activity. Nakao *et al*. (1968) found 60% of a DMD patient group (n = 80) had abnormal EEG recordings compared with 19% of a healthy school children control group (n = 16). They concluded that abnormal EEG recordings occur in a higher percentage of DMD patients than normal. Wayne and Browne-Mayers (1959), Kozicka *et al*. (1971), Black (1973) and Florek and Karolak (1977) do not indicate the precise nature of the EEG abnormalities they observed, which makes their findings difficult to interpret.

It remains unclear if there is a correlation between IQ and EEG abnormalities in the DMD boys. Perlstein *et al*. (1960) did find a correlation between these two factors, while Zellweger and Niedermeyer (1965), Kozicka *et al*. (1971), Black (1973) and Florek and Karolak (1977) found no correlation between EEG abnormalities and IQ. Nakao *et al*. (1968) mentions that patients with EEG abnormalities were 'more often inferior' in intelligence to those with normal recordings. Perlstein *et al*. (1960) found a correlation between increasing age and increasing EEG abnormalities. In contrast Zellweger and Niedermeyer (1965) found no correlation between disease progression and EEG abnormalities. Similarly Wayne and Browne-Mayers (1959) and Nakao *et al*. (1968) found no correlation between severity of disease and EEG abnormalities.

More recently Di Lazzario *et al*. (1998), using transcranial magnetic stimulation, reported that the excitability of the motor cortex is reduced in DMD patients (n = 4) compared with controls (n = 4). Central motor conduction time and excitability to electrical stimulation were unchanged in DMD patients, leading the authors to conclude that the reduction in motor cortex excitability in the DMD boys arose as a result of aberrant synaptic functioning, which is in agreement with biochemical evidence (Bresolin *et al*., 1994; Jueptner and Weiller, 1995).

In the mdx *mouse*

The *mdx* mouse has enabled rigorous electrophysiological investigation of functional abnormalities in the dystrophin deficient CNS. Full-length dystrophin is absent in hippocampal cells in the *mdx* mouse (Lidov *et al*., 1996) and functional deficits in these cells have been the subject of investigation in recent times. Both Mehler *et al*. (1992) and Godfraind *et al*. (2000) have demonstrated that CA1 hippocampal neurones display a significantly increased susceptibility to hypoxia-induced reduction in synaptic transmission at Schaffer collateral/commissural CA1 synapses. Interestingly, there is no difference in long-term potentiation in CA1 and dentate gyrus cells in *mdx* mice (10–12 weeks) compared with controls (Sesay *et al*., 1996; Godfraind *et al*., 1997).

Further studies have included another mouse model, the *mdx*^{3cv}, which lacks the Dp140 and Dp71 dystrophin isoforms, both of which are present in control and *mdx* brain tissue but lacking in many boys with Duchenne's. To this end, Vaillend *et al*. (1998) employed the brain slice technique to test synaptic plasticity in 21–24 week old *mdx* and *mdx*^{3cv} mice. In agreement with Sesay *et al*. (1996), they found no deficiency in synaptic transmission in either strain of *mdx* mice; however, post-tetanic potentiation was increased in *mdx* mice. Vaillend *et al*. (1999) went on to further characterize the difference in post-tetanic potentiation seen previously in the *mdx* mouse using brain slices from 3–5 month-old control and *mdx* mice. In contrast to their previous study, post-tetanic potentiation was not significantly different in the *mdx* mouse compared with controls when the NMDA receptor antagonist D-APV (D-2-amino-5-phosphonovalerate) was present. Because of the indication that the NMDA receptor was affected by the lack of dystrophin, *n*NOS (nitric oxide synthase)-specific activity was also implicated due to NOS activation via NMDA-receptor mediated elevation of intracellular calcium levels. Accordingly they evoked pre-synaptic fibre volleys and field excitatory post-synaptic potentials mediated through both NMDA receptors and non-NMDA receptors. They found comparable synaptic responses in both NMDA and non-NMDA receptor subtypes of *mdx* and control mice. This indicates normal glutamatergic neuronal transmission, and hence preserved *n*NOS activity. The authors argue that the differences seen in short-term potentiation are due to a post-synaptic rather than a pre-synaptic mechanism. Using voltage-gated calcium channel antagonists nifedipine and $NiCl_2$ they found no difference in potentiation in either *mdx* or control mice, indicating that these channels are not responsible for their observations.

Conclusion and clinical implications

In recent years there has been a substantial increase in our understanding of the role of dystrophin in the CNS. These studies have been largely carried out on DMD boys and the dystrophin deficient *mdx* mouse and have demonstrated a range of abnormalities in CNS function, from behavioural and cognitive dysfunction to alterations in the clustering of ion channels in single identified neurones.

The major clinical issue in DMD is the skeletal muscle pathology, and this has understandably received the greatest attention. There has been very little clinical investigation of the role of dystrophin in the CNS in DMD. However, with the dramatic increase in our understanding of this role over the last decade or so, as detailed in this review, there is now a sufficient body of data on the functions of dystrophin in the CNS, and the implications of its disruption, for its clinical relevance to begin to be appreciated.

This potential clinical relevance may best be illustrated by consideration of the potential impact of a disruption in the distribution and function of the inhibitory receptor $GABA_A$. A disruption of $GABA_A$ receptors may impact clinically in at least three areas: clinical efficacy of drugs, sleep disorders and motor control.

Many substances widely used in clinical medicine exert their influence exclusively or in part by binding to the $GABA_A$ receptor. It is now reasonably well established that substances such as barbiturates, benzodiazepines, anaesthetics and corticosteroids interact with the $GABA_A$ receptor in the CNS (for a review, see Johnston, 1996). If boys with DMD have an abnormality in distribution and function of these receptors then the efficacy of these substances could be altered. GABA disruption may also in part explain the sleep disorders suffered by many DMD boys. Sleep disorders in DMD are characterized by sleep fragmentation, increased arousal frequency and REM (rapid eye movement) sleep deprivation (Redding *et al*., 1985). Interestingly, a recent review on the role of GABA receptors in sleep regulation provides evidence suggesting that activation of $GABA_A$ receptors is crucial in both the initiation and maintenance of non-REM sleep and in the generation of sleep spindles (Lancel, 1999). Finally, the motor problems experienced by boys with DMD are, of course, due largely to the skeletal muscle pathology. A disruption of normal motor control function may also have an impact on the ability of DMD boys to learn and carry out movement, and to compensate for the structural deformities in skeletal muscle. The cerebellum is a part of the motor control system, and has been shown to play a major role in such aspects of motor behaviour as motor task automation, motor learning and timing functions associated with motor tasks (Ivry and Keel, 1985; Jenkins *et al*., 1994). As detailed above, the cerebellar Purkinje cells in the *mdx* mouse have a disruption in $GABA_A$ cluster size and, if a similar disruption occurs in DMD boys resulting in some abnormality in cerebellar function, it could influence their ability to learn and execute motor tasks. Although these three examples of possible clinical relevance of $GABA_A$ receptor abnormalities are speculative, they indicate the potential importance of an understanding of the role of dystrophin in the CNS to the clinical management of boys with DMD.

References

al-Qudah AA, Kobayashi J, Chuang S, Dennis M, Ray P. Etiology of intellectual impairment in Duchenne muscular dystrophy. Pediatr Neurol 1990; 6: 57–9.

Allen JE, Rodgin DW. Mental retardation in association with progressive dystrophy. Am J Dis Child 1960; 100: 208–11.

Anderson SW, Routh DK, Ionasescu VV. Serial position memory of boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1988; 30: 328–33.

Appleton RE, Bushby K, Gardner-Medwin D, Welch J, Kelly PJ. Head circumference and intellectual performance of patients with Duchenne muscular dystrophy. Dev Med Child Neurol 1991; 33: 884–90.

Ashley DL, Goldstein JH. In vitro erythrocyte water transport in Duchenne muscular dystrophy: an NMR investigation. Neurology 1983; 33: 1206–9.

Barbujani G, Russo A, Danieli GA, Spiegler AW, Borkowska J, Petrusewicz IH. Segregation anaylsis of 1885 DMD families. Significant departure from the expected proportion of sporadic cases. Hum Genet 1990; 84: 522–6.

Barwick DD, Osselton JW, Walton JN. Electroencephalographic studies in hereditary myopathy. J Neurol Neurosurg Psychiatry 1965; 28: 109–14.

Bates TE, Strangwald M, Keelan J, Davey GP, Munro PM, Clarke JB. Inhibition of N-acetylaspartate production. Implications for 1H MRS studies in vivo. Neuroreport 1996; 7: 1397–400.

Billard C, Gillet P, Barthez M, Hommet C, Bertrand P. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. Dev Med Child Neurol 1998; 40: 12–20.

Black FW. Intellectual ability as related to age and stage of disease in muscular dystrophy: a brief note. J Psychol 1973; 84: 333–4.

Blake DJ, Kröger S. The neurobiology of Duchenne muscular dystrophy: learning lessons from muscle? [Review]. Trends Neurosci 2000; 23: 92–9.

Boivin P. Homologies between membrane proteins result in expected or unexpected relation between neuromuscular and erythrocyte diseases. [Review]. [French]. Rev Med Interne 1992; 13: 156–61.

Bresolin N, Castelli E, Comi GP, Felisari G, Bardoni A, Perani D, et al. Cognitive impairment in Duchenne muscular dystrophy. Neuromuscul Disord 1994; 4: 359–69.

Bulfield G, Siller WG, Wight PA, Moore KJ. X chromosome-linked muscular dystrophy (mdx) in the mouse. Proc Natl Acad Sci USA 1984; 81: 1189–92.

Bushby KM. Genetic and clinical correlations of Xp21 muscular dystrophy. [Review]. J Inherit Metab Dis 1992; 15: 551–64.

Carretta D, Santarelli M, Vanni D, Carrai R, Sbriccoli A, Pinto F, et al. The organisation of spinal projecting brainstem neurons in an animal model of muscular dystrophy: a retrograde tracing study on mdx mutant mice. Brain Res 2001; 895: 213–22.

Castles A, Coltheart M. Varieties of developmental dyslexia. Cognition 1993; 47: 149–80.

Chen DH, Takeshima Y, Ishikawa Y, Ishikawa Y, Minami R, Matsuo M. A novel deletion of the dystrophin S-promoter region co-segregating with mental retardation. Neurology 1999; 52: 638–40.

Cohen HJ, Molnar GE, Taft LT. The genetic relationship of progressive muscular dystrophy (Duchenne type) and mental retardation. Dev Med Child Neurol 1968; 10: 754–65.

Desmond JE, Gabrieli JD, Wagner AD, Ginier BL, Glover GH. Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. J Neurosci 1997; 17: 9675–85.

Di Lazzaro V, Restuccia D, Servidei S, Nardone R, Oliviero A, Profice P, et al. Functional involvement of cerebral cortex in Duchenne muscular dystrophy. Muscle Nerve 1998; 21: 662–4.

Dorman C, Hurley AD, D'Avignon J. Language and learning disorders of older boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1988; 30: 316–27.

Dubowitz V. Intellectual impairment in muscular dystrophy. Arch Dis Child 1965; 40: 296–301.

Dubowitz V. Involvement of the nervous system in muscular dystrophies in man. Ann NY Acad Sci 1979; 317: 431–9.

Dubowitz V, Crome L. The central nervous system in Duchenne muscular dystrophy. Brain 1969; 92: 805–8.

Duchenne GBA. Recherches sur la paralysie musculaire pseudo-hypertrophique, ou paralysie myo-sclerosique. Arch Gen Med 1868; 11: 5–25 179–209, 305–21, 421–43, 552–88.

Duncan CJ. Dystrophin and the integrity of the sarcolemma in Duchenne muscular dystrophy. [Review]. Experientia 1989; 45: 175–7.

Emery AH. Population frequencies of inherited neuromuscular diseases—a world survey. Neuromuscul Disord 1991; 1: 19–29.

Ferretti G, Tangorra A, Curatola G. Effects of intramembrane particle aggregation on erythrocyte membrane fluidity: an electron spin resonance study in normal and in dystrophic subjects. Exp Cell Res 1990; 191: 14–21.

Florek M, Karolak S. Intelligence levels of patients with the Duchenne type of progressive muscular dystrophy (pmd-d). Eur J Pediatr 1977; 126: 275–82.

Frigeri A, Nicchia GP, Nico B, Quondamatteo F, Herken R, Roncali L, et al. Aquaporin-4 deficiency in skeletal muscle and brain of dystrophic mdx mice. FASEB J 2001; 15: 90–8.

Godfraind JM, Zizi M, Deconinck N. Hippocampal LTP in dystrophin and dystrophin-isoforms deficient mice [abstract]. Proc Soc Neurosci Abstr 1997; 23: 1874.

Godfraind JM, Tekkök SB, Krnjevic K. Hypoxia on hippocampal slices from mice deficient in dystrophin (mdx) and isoforms (mdx^{3cv}). J Cereb Blood Flow Metab 2000; 20: 145–52.

Gowers WR. Pseudo-hypertrophic muscular paralysis. London: J. & A. Churchill; 1879.

Griffin JL, Williams HJ, Sang E, Clarke K, Rae C, Nicholson JK. Metabolic profiling of genetic disorders: a multitissue 1H nuclear magnetic resonance spectroscopic and pattern recognition study into dystrophic tissue. Anal Biochem 2001; 293: 16–21.

Head SI. Membrane potential, resting calcium and calcium transients in isolated muscle fibres from normal and dystrophic mice. J Physiol (Lond) 1993; 469: 11–19.

Head SI, Williams DA, Stephenson DG. Abnormalities in structure and function of limb skeletal muscle fibres of dystrophic mdx mice. Proc R Soc Lond B Biol Sci 1992; 248: 163–9.

Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. Neurology 2000; 54: 2127–32.

Itoh K, Jinnai K, Tada K, Hara K, Itoh H, Takahashi K. Multifocal glial nodules in a case of Duchenne muscular dystrophy with severe mental retardation. Neuropathology 1999; 19: 322–7.

Ivry RB, Keele SW. Timing functions of the cerebellum. J Cogn Neurosci 1989; 1: 136–52.

Jagadha V, Becker LE. Brain morphology in Duchenne muscular dystrophy: a Golgi study. Pediatr Neurol 1988; 4: 87–92.

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994; 14: 3775–90.

Johnston GA. GABAA receptor pharmacology. [Review]. Pharmacol Ther 1996; 69: 173–98.

Jueptner M, Weiller C. Does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. [Review]. Neuroimage 1995; 2: 148–56.

Karagan NJ. Intellectual functioning in Duchenne muscular dystrophy: a review. [Review]. Psychol Bull 1979; 86: 250–9.

Karagan NJ, Zellweger HU. IQ studies in Duchenne muscular dystrophy II: test-retest performance [abstract]. Dev Med Child Neurol 1976; 18: 251.

Karagan NJ, Zellweger HU. Early verbal disability in children with Duchenne muscular dystrophy. Dev Med Child Neurol 1978; 20: 435–41.

Karagan NJ, Richman LC, Sorensen JP. Analysis of verbal disability in Duchenne muscular dystrophy. J Nerv Ment Dis 1980; 168: 419–23.

Kato T, Nishina M, Matsushita K, Hori E, Akaboshi S, Takashima S. Increased cerebral choline-compounds in Duchenne muscular dystrophy. Neuroreport 1997; 8: 1435–7.

Knuesel I, Mastrocola M, Zuellig RA, Bornhauser B, Schaub MC, Fritschy JM. Altered synaptic clustering of $GABA_A$ receptors in mice lacking dystrophin (mdx mice). Eur J Neurosci 1999; 11: 4457–62.

Koenig M, Hoffman EP, Bertelson CJ, Monaco EP, Feener C, Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell 1987; 50: 509–17.

Kozicka A, Prot J, Wasilewski R. Mental retardation in patients with Duchenne progressive muscular dystrophy. J Neurol Sci 1971; 14: 209–13.

Kunkle LM, Monaco AP, Middlesworth W, Ochs HD, Latt SA. Specific cloning of DNA fragments absent from the DNA of a male patient with an X chromosome deletion. Proc Natl Acad Sci USA 1985; 82: 4778–82.

Lancel M. Role of $GABA_A$ receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. [Review]. Sleep 1999; 22: 33–42.

Leibowitz D, Dubowitz V. Intellect and behaviour in Duchenne muscular dystrophy. Dev Med Child Neurol 1981; 23: 577–90.

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 Genet 1993; 2: 1877–81.

Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children. Cerebellar cognitive affective syndrome in a paediatric population. Brain 2000; 123: 1041–50.

Lidov HG. Dystrophin in the nervous system. [Review]. Brain Pathol 1996; 6: 63–77.

Lincoln NB, Staples DJ. Psychological aspects of some chronic progressive neuromuscular disorders. 1. Cognitive abilities. J Chronic Dis 1977; 30: 207–15.

Marsh GG, Munsat TL. Evidence for early impairment of verbal intelligence in Duchenne muscular dystrophy. Arch Dis Child 1974; 49: 118–22.

Mehler MF. Brain dystrophin, neurogenetics and mental retardation. [Review]. Brain Res Brain Res Rev 2000; 32: 277–307.

Mehler MF, Haas KZ, Kessler JA, Stanton PK. Enhanced sensitivity of hippocampal pyramidal neurons from mdx mice to hypoxia-induced loss of synaptic transmission. Proc Natl Acad Sci USA 1992; 89: 2461–5.

Menke A, Jockusch H. Decreased osmotic stability of dystrophin-less muscle cells from the mdx mouse. Nature 1991; 349: 69–71.

Misuri G, Lanini B, Gigliotti F, Iandelli I, Pizzi A, Bertolini MG, et al. Mechanism of CO2 retention in patients with neuromuscular disease. Chest 2000; 117: 447–53.

Moizard MP, Toutain A, Fournier D, Berret F, Raynaud M, Billard C, et al. Severe cognitive impairment in DMD: obvious clinical indication for Dp71 isoform point mutation screening. Eur J Hum Genet 2000; 8: 552–6.

Morrow RS, Cohen J. The psychosocial factors in muscular dystrophy. J Child Psychol Psychiatry 1954; 3: 70–80.

Muir JK, Lobner D, Monyer H, Choi DW. $GABA_A$ receptor activation attenuates excitotoxicity but exacerbates oxygen-glucose deprivation-induced neuronal injury in vitro. J Cereb Blood Flow Metab 1996; 16: 1211–18.

Muntoni F, Mateddu A, Serra G. Passive avoidance behaviour deficit in the mdx mouse. Neuromuscul Disord 1991; 1: 121–3.

Nakao K, Kito S, Muro T, Tomonaga M, Mozai T. Nervous system involvement in progressive muscular dystrophy. Proc Aust Assoc Neurol 1968; 4: 557–64.

Nicolson RI, Fawcett AJ, Berry EL, Jenkins IH, Dean P, Brooks DJ. Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. Lancet 1999; 353: 1662–7.

Perlstein MA, Gibbs FA, Gibbs EL, Stein MD. Electroencephalogram and myopathy. Relation between muscular dystrophy and related diseases. JAMA 1960; 173: 1329–33.

Poser CM, Ziegler DK. Clinical significance of 14 and 6 per second positive spike complexes. Neurology 1958; 8: 903–12.

Prosser EJ, Murphy EG, Thompson MW. Intelligence and the gene for Duchenne muscular dystrophy. Arch Dis Child 1969; 44: 221–30.

Pulido SM, Passaquin AC, Leijendekker WJ, Challet C, Wallimann T, Ruegg UT. Creatine supplementation improves intracellular Ca2+ handling and survival in mdx skeletal muscle cells. FEBS Lett 1998; 439: 357–62.

Rae C, Griffin JL, Bothwell JH. Metabolic abnormalities in the mdx mouse brain. Proc Aus Biochem Soc Mol Biol 1998a; 30: 176.

Rae C, Scott RB, Thompson CH, Dixon RM, Dumughn I, Kemp GJ, et al. Brain biochemistry in Duchenne muscular dystrophy: a 1H magnetic resonance and neuropsychological study. J Neurol Sci 1998b; 160: 148–57.

Rae C, Lee MA, Dixon RM, Blamire AM, Thompson CH, Styles P, et al. Metabolic abnormalities in the developmental dyslexia detected by 1H magnetic resonance spectroscopy. Lancet 1998c; 351: 1849–52.

Rae C, Blair DH, Griffin JL, Bothwell JHF, Bubb WA, Maitland A, et al. Brain biochemical abnormalities associated with lack of dystrophin; studies in the mdx mouse. Neuromuscul Disord. In press 2001.

Rapaport D, Passos-Bueno MR, Brandão L, Love D, Vainzof M, Zatz M. Apparent association of mental retardation and specific patterns of deletions screened with probes cf56a and cf23a in Duchenne muscular dystrophy. Am J Med Genet 1991; 39: 437–41.

Ray PN, Belfall B, Duff C, Logan C, Kean V, Thompson MW, et al. Cloning of the breakpoint of an X;21 translocation associated with Duchenne muscular dystrophy. Nature 1985; 318: 672–5.

Redding GJ, Okamoto GA, Guthrie RD, Rollevson D, Milstein JM. Sleep patterns in nonambulatory boys with Duchenne muscular dystrophy. Arch Phys Med Rehabil 1985; 66: 818–21.

Roses AD, Appel SH. Erythrocyte spectrin peak II phosphorylation in Duchenne muscular dystrophy. J Neurol Sci 1976; 29: 185–93.

Roses AD, Herbstreith MH, Appel SH. Membrane protein kinase alteration in Duchenne muscular dystrophy. Nature 1975; 254: 350–1.

Rosman NP. The cerebral defect and myopathy in Duchenne muscular dystrophy. A comparative and clinicopathological study. Neurology 1970; 20: 329–35.

Rosman NP, Kakulas BA. Mental deficiency associated with muscular dystrophy. A neuropathological study. Brain 1966; 89: 769–88.

Sbriccoli A, Santarelli M, Carretta D, Pinto F, Granato A, Minciacchi D. Architectural changes of the cortico-spinal system in the dystrophin defective mdx mouse. Neurosci Lett 1995; 200: 53–6.

Scheinfeld A. The new you and heredity. Philadelphia: J. B. Lippincott; 1950. p. 314.

Schmidt B, Watters GV, Rosenblatt B, Silver K. Increased head circumference in patients with Duchenne muscular dystrophy. Ann Neurol 1985; 17: 620–1.

Schoelly ML, Fraser AW. Emotional reactions in muscular dystrophy. Am J Phys Med 1955; 34: 119–23.

Septien L, Gras P, Borsotti JP, Giroud M, Nivelon JL, Dumas R. Le développement mental dans dystrophie musculaire de Duchenne. Corrélation avec les données du scanner cérébral. Pediatrie 1991; 46: 817–19.

Serbu AM, Marian A, Popescu O, Pop VI, Borza V, Benga I, Benga G. Decreased water permeability of erythrocyte membranes in

patients with Duchenne muscular dystrophy. Muscle Nerve 1986; 9: 243–7.

Sesay AK, Errington ML, Levita L, Bliss TV. Spatial learning and hippocampal long-term potentiation are not impaired in mdx mice. Neurosci Lett 1996; 211: 207–10.

Sherwin AC, McCully RS. Reactions observed in boys of various ages (ten to fourteen) to a crippling, progressive, and fatal illness (muscular dystrophy). J Chron Dis 1961; 13: 59–68.

Smith RA, Sibert JR, Harper PS. Early development of boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1990; 32: 519–27.

Sollee ND, Latham EE, Kindlon DJ, Bresnan MJ. Neuropsychological impairment in Duchenne muscular dystrophy. J Clin Exp Neuropsychol 1985; 7: 486–96.

Strange K, Morrison R, Shrode L, Putnam R. Mechanism and regulation of swelling-activated inositol efflux in brain glial cells. Am J Physiol 1993; 265: C244–56.

Tarnopolsky MA, Parise G. Direct measurement of high-energy phosphate compounds in patients with neuromuscular disease. Muscle Nerve 1999; 22: 1228–33.

Torres LF, Duchen LW. The mutant mdx: inherited myopathy in the mouse. Morphological studies of nerves, muscles and end-plates. Brain 1987; 110: 269–99.

Tracey I, Scott RB, Thompson CH, Dunn JF, Barnes PR, Styles P, et al. Brain abnormalities in Duchenne muscular dystrophy: phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. Lancet 1995; 345: 1260–4.

Tracey I, Dunn JF, Radda GK. Brain metabolism is abnormal in the mdx model of Duchenne muscular dystrophy. Brain 1996a; 119: 1039–44.

Tracey I, Dunn JF, Parkes HG, Radda GK. An in vivo and in vitro 1H-magnetic resonance spectroscopy study of mdx mouse brain: abnormal development or neural necrosis? J Neurol Sci 1996b; 141: 13–18.

Truitt CL. Personal and social adjustments of children with muscular dystrophy. Am J Phys Med 1955; 34: 124–8.

Vaillend C, Rendon A, Misslin R, Ungerer A. Influence of dystrophin-gene mutation on mdx mouse behavior. I. Retention deficits at long delays in spontaneous alternation and bar-pressing tasks. Behav Genet 1995; 25: 569–79.

Vaillend C, Billard J-M, Claudepierre T, Rendon A, Dutar P, Ungerer A. Spatial discrimination learning and CA1 hippocampal synaptic plasticity in mdx and mdx^{3cv} mice lacking dystrophin gene products. Neuroscience 1998; 86: 53–66.

Vaillend C, Ungerer A, Billard J-M. Facilitated NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. Synapse 1999; 33: 59–70.

Walton JN, Nattrass FJ. On the classification, natural history and treatment of the myopathies. Brain 1954; 77: 169–231.

Wayne HL, Browne-Mayers AN. Clinical and EEG observations in patients with progressive muscular dystrophy. Dis Nerv Syst 1959; 20: 288–91.

Worden DK, Vignos PJ. Intellectual function in childhood progressive muscular dystrophy. Pediatrics 1962; 29: 968–77.

Wrogemann K, Pena SD. Mitochondrial calcium overload: a general mechanism for cell necrosis in muscle diseases. Lancet 1976; 1: 672–4.

Yoshioka M, Okuna T, Honda Y, Nakano Y. Central nervous system involvement in progressive muscular dystrophy. Arch Dis Child 1980; 55: 589–94.

Zellweger H, Hanson JW. Psychometric studies in muscular dystrophy type 3a (Duchenne). Dev Med Child Neurol 1967; 9: 576–81.

Zellweger H, Niedermeyer E. Central nervous system manifestations in childhood muscular dystrophy (CMD). I. Psychometric and electroencephalographic findings. Ann Paediat 1965; 205: 25–42.

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