Review
Combining genetics, neuropsychology and neuroimaging to improve understanding of brain involvement in Duchenne muscular dystrophy - a narrative review

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Abstract

Duchenne muscular dystrophy is a multifactorial disease including a cognitive phenotype. It is caused by mutations in the X-chromosomal DMD gene from which dystrophin is synthesized. Multiple isoforms of dystrophin have been identified. The full length dystrophin isoform Dp427m is expressed predominantly in muscle. Other isoforms include: Dp427c, Dp427p, Dp260, Dp140, Dp116, Dp71 and Dp40. The majority of these isoforms are expressed in brain and several hypotheses exist on their role in subtypes of neurons and astrocytes. However, their function in relation to cognition remains unclear. Unlike progressive muscle wasting, cognitive involvement is not seen in all DMD patients and the severity varies greatly. To achieve a better understanding of brain involvement in DMD, a multidisciplinary approach is required. Here, we review the latest findings on dystrophin isoform expression in the brain; specific DMD-associated learning and behavioural difficulties; and imaging and spectroscopy findings relating to brain structure, networks, perfusion and metabolism. The main challenge lies in determining links between these different findings. If we can determine which factors play a role in the differentiation between severe and minor cognitive problems in DMD in the near future, we can both provide better advise for the patients and also develop targeted therapeutic interventions.

Keywords: Duchenne muscular dystrophy; Dystrophin; Cognition; Neuroimaging.

1. Introduction

Studies have shown that learning and behavioural difficulties are not seen in all Duchenne muscular dystrophy (DMD) patients, and when they are reported the severity varies greatly [1–4]; this is in contrast to the condition of progressive muscle wasting which is universal. To people living with DMD, brain comorbidities can in fact have a greater impact on the family than limited mobility [5]. There is an acute need for a better understanding of the origin of the cognitive phenotype so that better advice can be provided, learning aids can to be developed or made available, and to determine where appropriate neuropsychopharmacology can be utilized [5]. A multidisciplinary approach is required to determine the origin of learning and behavioral difficulties, and there are still many challenges to overcome. This is the topic of this narrative review. In particular, we believe the following topics need to be addressed: specific learning and behavioural difficulties, but also specific strengths need to be well characterized; the brain regions that do and do not express dystrophin need to be mapped out; the function of dystrophin in the brain needs to be determined at a molecular level, but also in relation to brain networks; the differences in dystrophin expression across development need to be examined to determine if they can provide additional insight into the role of dystrophin in the brain; state-of-the-art neuroimaging techniques need to be employed to assess structural, perfusion or network differences in the brain in

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DMD as compared to their peers of all ages; finally, an understanding of how the cognitive profile is linked to the expression of dystrophin in the brain, and how both are linked to the neuroimaging results needs to be established. The overall determination of which factors play a role in the differentiation between severe/minor to even absence of cognitive or behavioral problems in DMD will enable better care for patients, and the development of effective targeted therapeutic interventions.

2. Dystrophin expression in the human brain

Within the DMD gene, there are at least seven promotors and at least eight dystrophin isoforms (Dp260, Dp140, Dp116, Dp71 and Dp40) [6–10]. These isoforms are named to reflect their relative size, and are expressed in different tissue types (Fig. 1). Bladen et al. reported that 68% of patients have a large deletion and 11% of patients have a large duplication mutation within the DMD gene [11]. The authors also showed that there is a deletion hotspot at exon 45–55 and a duplication hotspot at exon 2–22. With respect to the dystrophin isoforms expressed in brain, a mutation at the proximal end (exon 1–43) is predicted to result in the absence of Dp427p,c,m only, whereas more distal mutations (intron 44-exon 79) can additionally affect Dp140 or Dp71/Dp40. The aforementioned mutation hotspots together with the deletion/duplication incidences result in roughly half of the patients missing only Dp427, and half missing both Dp427 and Dp140. Only a very small number of patients will have a mutation that will also affect Dp71/Dp40.

The vast majority of our understanding of where dystrophin is expressed in the brain is derived from animal models, particularly the mdx mouse model [12]. For years, the main brain regions with dystrophin expression were considered to be the cortex, hippocampus, amygdala and cerebellum. Recently, the Allen Brain Atlas adult human brain and developing brain datasets were mined for DMD gene expression and DMD exon expression [13]. In the adult dataset, the six donor brains (five male, one female, aged 24–57, mean age 42 years) were segmented into 363 to 946 brain regions (3702 samples in total) [14]. The individual nuclei of the amygdala and the sub-regions of the hippocampus (i.e. CA1, CA2, CA3 and dentate gyrus) were able to be sampled separately. The resulting detailed map of dystrophin expression in the human brain shows relatively high expression in the amygdala (n = 67 samples) and hippocampus (n = 118 samples) and low expression in the pons (n = 165 samples) and cerebellum (n = 368 samples) [13]. An average degree of DMD expression was found throughout the cortex, with the temporal and frontal cortex having slightly higher expression than the parietal and occipital cortex. Expression in the amygdala, hippocampus and cortex seems consistent between species. However, the low expression in the cerebellum in human brain tissue is opposite to what is seen in mice, where there is high expression in the cerebellum. Much of the human DMD brain research has focused on the cerebellum in particular in the past [15–17], but based on these latest findings, the amygdala, hippocampus and cerebral cortex require more attention to relate the distribution of dystrophin to the cognitive phenotype.

In addition to the distribution of dystrophin expression in different brain regions there are two additional components to consider; the isoforms and developmental changes. Holder et al. [10] have suggested that promoter activation could vary with development. Compared with the adult dataset, the Allen Brain Atlas developing brain dataset contained many more, 42, donor brains [18]. It has an age range of eight weeks post-conception to 40 years of age, enabling the determination of DMD expression from very early stages, through birth, early childhood, adolescence and into adulthood. The trade-off is that these brains were segmented into a smaller number of

Fig. 1. (adapted from [12] and used with permission from A.M. Aartsma-Rus). An illustration of full length dystrophin (Dp427) protein is shown, with binding domains (BD) for among others actin (ABD), neuronal nitric oxide synthase (nNOS) and dystroglycan. The relative positions of the dystrophin isoform first exons within the DMD gene and corresponding protein are indicated below. Dp427p,c,m. Dp140 and Dp71/Dp40 are expressed in the brain. Dp260 is predominantly expressed in the retina and Dp116 is predominantly expressed in de peripheral nerve.
brain regions than the adult dataset. This is partially due to the size of the brain, which was for example very small at eight weeks post-conception, but also due to the fact that the analyses were performed for all exons, which is much more extensive. The data per exon is of great added value. Since the different dystrophin isoforms have a unique first exon (the first exon is not part of any of the other dystrophin isoforms), this data enabled the mapping of the isoforms separately and per developmental stage. The result was striking, as a clear distinction between isoforms becomes apparent [13]. Full length dystrophin expression was relatively low at all life stages; Dp71 had intermediate expression at all life stages; very little or no expression of Dp260 and Dp116 was found in these brain samples; and finally Dp140 was especially high during early development prior to birth. Interestingly, this fetal expression of Dp140 is consistent with early studies of western blot analysis in 3.5-month old fetal and 60-year old brain samples where Dp140 was only detected in the fetal sample [19].

When comparing the expression pattern of Dp427, Dp140 and Dp71, across development to all other genes in the database (19,991 genes in total), the top 1% of correlating genes was further investigated to generate new hypotheses of possible function of the different isoforms in the brain [13]. The functions “transmembrane transporter activity” and “synaptic transmission” and cellular position, as well as “neuron part” and “synaptic membrane” that emerged for the Dp427 network fitted well with what was found in preclinical studies [20–23]. These studies have demonstrated that Dp427 anchors GABA_A receptors to the post-synaptic membrane of GABAergic neurons. Absence of dystrophin resulted in a displacement of GABA_A receptors.

Much less is known concerning the function of Dp140, which is often grouped together with Dp71. Within the Dp140 network, the functions were “transcription factor activity”, “dendrite development”, “neuron differentiation” and “chromatin modification”. There was no clear cellular position but the functions point towards a role in early developmental biology. In contrast, the network for Dp71/Dp40 was associated with “vascular development” and “cell motility” with an extracelluar localization or a link between the “cell surface” and “extracellular matrix”. There is preclinical data that also points towards a role for Dp71 in the cerebral vasculature [24,25]. More specifically, Dp71 is found at the specialized end-feet processes of perivascular astrocytes, where they cluster and co-purify with aquaporon-4 (ACP4) channels. However, there is also preclinical evidence that Dp71 has a role in neuron differentiation which is more in line with what was found for Dp140 [26,27].

Even though we now have a better understanding of when and where dystrophin is expressed in the human brain, the above hypotheses concerning the function of the dystrophin isoforms still need to be tested. And importantly, what has not yet been investigated are the multiple splice variants of each of the isoforms that may well have specialist functions, and need to be investigated at the protein, rather than RNA, level.

3. Cognition and behavior

Learning and behavioral problems in DMD [2,3,28,29], can occur both in patients with cognitive impairment and in those with IQs in the normal to high range [4], and can be detected early in development [30]. A one-standard-deviation shift in full scale IQ (mean=85) for DMD compared with the general population is reported consistently [31–34]. Specific difficulties have been described with respect to information processing, (verbal) working memory, and reading. In addition, there are numerous reports on comorbidities such as autism spectrum disorder (ASD) 3–15%, attention deficit hyper activity disorder (ADHD) 11–32%, obsessive compulsive disorder (OCD) 5–60%, anxiety 27% and epilepsy 6% [3,17,28–30,35–37]. However, patients with DMD are not consistently screened for learning or behavioral problems, and when they are, a variety of different diagnostic instruments are employed. A diagnostic test battery specific for DMD has not yet been established. Once it is, the incidence and severity of the cognitive profile can be better characterized. This is an essential step to come to an understanding of the potential links between dystrophin isoforms and the cognitive profile.

4. Neuropathy

There are several classical reports on postmortem evaluation of the brain in DMD. For example, Rosman and Kakulas [38] compared three patients diagnosed with DMD and intellectual impairment to a control group of patients with DMD without intellectual impairment and found several cerebral abnormalities associated with the cognitive phenotype. The DMD patients with intellectual impairment had lower total brain weight and increased cortical thickness, with fewer neurons, poor layering and misplaced cells. Only one of the three had gross structural abnormalities, but all had microscopic alterations. Subsequently, Dubowitz and Crome [39] performed postmortem evaluation of the brain in 21 DMD patients. They found brain weight within the normal range for all except one patient. No gross structural abnormalities were found and only marginally diffuse neuronal loss was seen. Histological abnormalities were reported for six patients. No clear relationship with cognitive abilities was found, in contrast to results reported previously. Several years later Jagadha and Becker [40] performed postmortem evaluation of the brain in another thirteen DMD patients. Similarly, they found no gross structural abnormalities and the brain weight was in the normal range for all except one patient. This one patient also had intellectual impairment, neuronal loss and astrogliosis. Three patients were further examined and abnormal dendrite development and arborization patterns were found. The conclusion of such studies indicate that the brain involvement in DMD is not uniform. In general, no gross structural abnormalities are inherent; however, specific histological abnormalities can be found in individual DMD patients.
5. Neuroimaging

A summary of neuroimaging findings in DMD is shown in Fig. 2. The first reports on neuroimaging in DMD were obtained with CT [41]. Thirty patients were scanned, ten of whom had an IQ below 70. Slight cerebral atrophy was found in 67%, 60% had slight ventricular dilation, and 30% had cortical atrophy. There was no correlation of age with IQ, but the older patients did have more severe cortical atrophy. Ten years later, slight cortical atrophy was also found in an MRI study in two out of four patients [42]. In line with this, lower total brain and gray matter volume compared to age-matched healthy controls were found in a quantitative MRI study (n = 29 DMD patients) [43]. The same study also found altered white matter microstructure. The exact origin of the altered white matter microstructure would have required postmortem evaluation; however, even without this evaluation these findings are in line with abnormal dendrite development previously reported. Alternatively, they could also indicate myelin damage or altered structural connectivity.

Reduced glucose metabolism was later found with PET in four patients [1]. In all patients, the metabolic reduction was found in both cerebellar hemispheres. Hypometabolism in the left frontal and parietal associative cortices and, bilaterally, in the temporal and occipital cortex, was a consistent pattern in one patient, who also had severe cognitive impairment (IQ = 58). One patient had right parietal and temporal hypometabolism and bilateral occipital metabolic reduction and one patient showed only a bilateral occipital hypometabolism, together with cerebellar involvement. Glucose hypometabolism in DMD was further confirmed in the sensori-motor area, temporal neocortex, medial temporal structures and cerebellum in ten DMD patients [44].

Reduced cerebral perfusion was subsequently reported in the same study cohort in which reduced gray matter volume was found [45]: however, these two findings were unrelated pointing towards several underlying mechanisms. Reductions were uniformly spread throughout the brain. Patients who were predicted to miss not only Dp427, but Dp140 as well, had lower end gray matter volumes and lower cerebral perfusion.

6. Connecting the dots: missing pieces of the puzzle

Using all methods at our disposal is going to be key for determining which factors play a role in the differentiation between severe/ minor or even absence of cognitive problems in DMD. As it stands, a genotype-phenotype association seems to provide a partial explanation for the differences between patients. Ricotti et al. [46] reported on the association between distal or proximal mutations within the DMD gene and the neurocognitive profile in 87 patients. They found a clustering of symptoms, where often 2–4 comorbidities were reported for a single patient. Patients with a distal mutation had a higher incidence of neurodevelopmental problems, intellectual disability and working memory deficits. Similarly, reductions in gray matter volume and cerebral perfusion were more profound in patients with distal mutations. If indeed the dystrophin isoforms play different roles throughout development as suggested by the Allen Brain Atlas data and preclinical studies, then it is plausible that the absence of multiple isoforms results in a greater risk of cognitive deficits.
However, Ricotti et al. [46] also found that emotional and behavioral difficulties were evenly distributed among patients with proximal or distal mutations. Similarly, the genotype-phenotype neuroimaging association that was evident on a group level, could not be confirmed on an individual patient level [43]. For example, a patient with one of the lowest gray matter volumes had an IQ of 114 and had graduated from university with honours. At the same time, a patient with general developmental delay, autism spectrum disorder and epilepsy had a normal range gray matter volume.

In addition to the uncorrelated gray matter volumes and cerebral perfusion, this inconsistency in genotype-phenotype associations also suggests that there may be multiple mechanisms at play, relating to different aspects of the cognitive profile in DMD. This concept is supported by the various functions suggested by the gene-correlation analyses. For example, Dp427 which is missing in all patients, is potentially linked to the emotional and behavioral problems which could be caused by misplaced signaling receptors in specific neurons, with the amygdala and hippocampus being regions of interest. The cognitive problems are then potentially related to Dp140 or Dp71. In particular, the high expression of Dp140 during early development, and its suggested roles such as neuronal differentiation point towards an key role early in life. In addition, both Dp140 and Dp71 are hypothesized to be involved in the cerebral vasculature, either directly or indirectly. The exact connection to cognition remains to be resolved, but low cerebral perfusion has been associated with lower IQ in normally developing children [47]. Specifically in DMD, however, other factors to consider with respect to the reduced cerebral blood flow include cardiac function, limited mobility and dystrophin in the vasculature itself.

Alternatively, the emotional and behavioral problems can also be secondary effects due to any of the numerous consistent factors among all patients, such as for example the use of corticosteroids which has not been systematically investigated. It is also unknown what happens to the shorter isoforms in the absence of Dp427; Dp140 or Dp71 could be up- or downregulated in response making it more difficult to separate individual effects.

Determining if there is a causal role for dystrophin isoforms for specific elements of the cognitive profile will be instrumental for future care guidelines and therapy design.

A final missing piece of the puzzle to discuss, which is instrumental to understanding the pathophysiology, is whether or not the cognitive phenotype is progressive. From the cross-sectional studies, most reports indicate no correlation with age suggesting that there is no progression in terms of neurocognitive decline. However, the CT neuroimaging reports suggest progressive neurodegeneration with the older patients showing more severe cortical atrophy, albeit without an association with poorer cognitive function. Treatment strategies that address developmental delay may differ greatly from those addressing neurodegeneration. Therefore there is an urgent need for longitudinal studies to address this large unknown. By systematic follow-up of patients over time it should be possible to address the inherently low study population of a rare disorder, the great diversity in individual phenotypes, and the relatively high natural variability in neuroimaging measurements.

In summary, important first steps have been made, but there is still much to be done to obtain a better understanding of the origin of the cognitive phenotype so that better patient advice can be provided, learning aids can to be developed or made available and, where applicable, neuropsychopharmacology can be utilized.

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