(6MWT) was compared to two shorter ambulatory assessments: 2-min walk test (2MWT), and 100 m walk/run test (100 m). The 2MWT was completed according to 6MWT guidelines but lasted only 2-min; whereas the 100 m allowed subjects to complete two 50-m laps as quickly as possible, including running if able. Maximum voluntary isometric strength of hip and knee muscles was assessed using a hand-held dynamometer. The 2MWT and 100 m were highly correlated with 6MWT ($r = 0.827$ and $r = -0.827$ respectively, $p = 0.002$). The 100 m was most highly correlated with lower extremity strength measures and other functional outcomes. A shorter timed walking or running test may be beneficial for use in clinical trials in children with Duchenne muscular dystrophy. The 2MWT or 100 m may decrease individual variability seen in the 6MWT due to shorter walking time or a concrete fixed distance. Further research is needed to determine which ambulatory assessments are most valid, reliable, and sensitive to change over time.

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P.2.11
CINRG Duchenne Natural History Study: Relationship of longitudinal measures of ambulatory timed function tests and loss of clinical milestones
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The Cooperative International Neuromuscular Research Group (CINRG) DMD Natural History Study enrolled 340 individuals with DMD aged 2–28 years in a longitudinal observational study. Clinical assessments were obtained every 3 months for the first year and annually thereafter. The aim of this sub analysis was to evaluate the predictive capabilities of timed tests in assessing loss of clinically meaningful milestones.

We created a 6-level composite of individual “milestone” tasks combining the results from the ability to perform the timed function tests and the Brooke and Vignos functional scales. Three GC groups (naive, current user, past user) were compared on timed function velocities at ages <4, 4–6, 7–9, 10–12, and 13–15. Kaplan Meier survival analysis was used to evaluate the degree to which loss of clinically meaningful milestones are predicted by time function tests.

Timed function velocities increased with age in children <7 years and decrease thereafter.Velocities were higher in those treated with GC across all age ranges. Over 12 months, Time to Stand >10 s. predicted loss of ability to stand ($log\text{rank } p < 0.0001$), and loss of standing ability predicted loss of ability to climb stairs, and walk independently ($log\text{rank } p < 0.0001$). Time to climb 4 stairs >8 s. predicted loss of stair climbing ($log\text{rank } p < 0.0001$), and loss of stair climbing predicted loss of ambulation ($log\text{rank } p < 0.0001$). The 10 m run/walk times of 6–11 s and >12 s. predicts loss of ambulation over 12 months ($log\text{rank } p < 0.0001$). Additionally, decline in walking velocity of >10% over a year predicted the likeliness of loss of ambulation over the following 4 years ($log\text{rank } p < 0.0001$).

Longitudinal studies of timed function tests show predictable maturational changes and improved timed function velocities in those currently treated with GC. Timed function tests are clinically meaningful in terms of predictive ability for loss of function.

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P.2.12
The Duchenne brain: A matter of grey and white
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Learning and behavioral problems are common in Duchenne muscular dystrophy (DMD) patients. In normal brain, various dystrophin isoforms are expressed, but little is known about their function. Cortical atrophy and disordered architecture have been reported in post mortem and CT scan studies. Since MRI is currently the most advanced technique to provide detailed morphological information of the brain, we performed structural MRI in 35 boys with DMD and 22 healthy age-matched controls (age 8–18 years). Three-dimensional T1-weighted scans were obtained for quantitative volume measurements. Diffusion tensor images (DTI) were obtained as a measure of structural integrity of the white matter. Localization of volumetric differences was assessed with voxel-based morphometry analysis. A cognitive profile of the boys was evaluated and found to be representative of the Dutch DMD population. Total brain volume was significantly smaller in DMD both before and after correcting for intracranial volume. Grey matter volume was also smaller in DMD and we found no focal differences in grey matter, suggesting an overall deficiency in neuronal cell bodies. The white matter volume in DMD was similar to controls. Throughout the white matter tracts, DTI showed lower fractional anisotropy (FA) in DMD indicating lower directionality of the neuronal fiber tracts. DTI also showed higher mean diffusivity (MD) in DMD. Lower FA and higher MD indicate reduced fiber density, increased membrane permeability and/or increased structural disorganization. These correspond with altered white matter integrity.

In summary, our findings show that both the grey matter and white matter are affected in DMD, with a reduction in volume in the grey matter and altered integrity of the white matter. Future analyses will correlate these morphological abnormalities to cognitive function and behavioral problems.

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P.2.13
Neuropsychiatric comorbidities in Duchenne Muscular Dystrophy
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Amongst boys with DMD, IQ is on average ~1 SD below the general population mean, with working memory impairments being especially prominent. We previously described that 25% of DMD boys present with clinically significant traits of Autistic Spectrum Disorder (ASD) and 35% of DMD boys meet the criteria for ADHD. Other comorbid psychopathologies include internalising (27%) and externalising (15%) behavioural problems. The objectives of our study were to describe to what extent neuropsychiatric comorbidities coexist in the
same individuals, and to describe the bearing that the genotype has on the neuropsychiatric phenotype in DMD. We recruited 98 DMD boys (70 in GOSH-UK and 28 in Italy), who underwent standardised neuropsychological assessments including: WISC-IV, 3Di, Conners-3 Questionnaires, and CBCL. We report that 75% of children with ASD also meet criteria for ADHD; of the DMD boys with ASD 53% had externalising behavioural problems. Half of the boys with ADHD also met criteria for ASD, externalising and internalising behavioural problems. There was a significant coexistence of psychiatric comorbidities in boys with mutations disrupting the shorter C-terminus dystrophin isoforms (Dp260, Dp140, Dp116, Dp71) when compared with mutations at the 5' end of the gene (p = 0.02). We demonstrated that neurodevelopmental disorders are highly prevalent in DMD. Boys with mutations downstream of exon 30 are at a higher risk of suffering from coexistence of neuropsychiatric symptoms, more commonly than what observed in the general psychiatric population. These findings suggest that DMD may have a distinctive neurodevelopmental profile, requiring targeted support.

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P.2.14
Isolated cognitive abnormalities associated to DMD mutations
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The dystrophinopathies are a group of X-linked muscle diseases caused by mutations in the DMD gene. Clinical phenotypes vary from asymptomatic high CK levels and cramps to severe progressive skeletal and cardiac muscle disorders such as Duchenne (DMD) and Becker (BMD) muscular dystrophies, and X-linked dilated cardiomyopathy (XLCM). About one third of patients present mental retardation. Most disease-responsible mutations are large intragenic rearrangements (exonic deletions and duplications) that account for 65–75% of cases, while the remaining cases are caused by single point mutations or small rearrangements [3,4]. In most patients, the clinical outcome can be predicted according to the reading-frame rule. The majority of DMD patients carry truncating mutations while BMD patients usually carry in-frame mutations allowing the expression of semi-functional dystrophins.

We present a male patient 23 years old with mental retardation and no muscle weakness. The Western blot with Dys 1 and Dys 2 antibodies showed a reduced amount of dystrophin. An Inframe deletion of exons 56 and 57 was identified by MLPA and cDNA sequencing, affecting different dystrophin isoforms: Dp424m, Dp260, Dp140 and Dp116. In addition, we diagnosed three symptomatic female carriers of dystrophinopathy presenting isolated cognitive abnormalities without muscle involvement. Each of them carried DMD mutations (Duplication exons 13-27, Subexonic deletion exon 46 and Deletion exons 46–55, respectively). A study of X-chromosome inactivation was performed exhibiting a clear bias in the inactivation of the paternal chromosome: 99:1, 88:12 and 100:0, respectively. These cases suggest that isolated mental retardation could be more frequent than expected.

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P.2.15
Expectations and decision making in clinical trials for Duchenne and Becker muscular dystrophy
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Increased community knowledge of and access to clinical trials for Duchenne and Becker muscular dystrophy (DBMD) may amplify adaptive optimism, but also inappropriately high expectations. This study explored parental and clinician motivations and expectations for DBMD clinical trials. We interviewed 15 parents of children with DBMD and 11 clinicians participating in 10 clinical trials for DBMD. Interviews were transcribed and coded for thematic analysis.

All parents hoped for, and most expected, direct benefit to their child; this was their primary motivator. Other motivators were a desire to affect the disease course; that “doing something is better than nothing;” and altruism. Most parents actively sought out a trial and described making their decision before the informed consent process (IC). The majority hoped for a cure but recognized this as unrealistic. Parents’ reported expectations were inconsistent in different contexts during the interviews. Some had difficulty differentiating between expectations and optimistic hopes. Some reported efforts to temper their expectations, or outside factors tempering expectations such as being in a placebo-controlled trial. Many parents described changes to expectations and hopes over time.

Clinicians reported that families were motivated by desperation and hope for benefit. Altruism was a less important motivator. Clinicians’ motivations included optimism, enthusiasm for having more to offer, and personal commitment. Clinicians’ expectations ranged from modest gains in knowledge to clinical improvement.

This study suggests the importance of interventions that help parents clarify expectations and identify inappropriately high expectations, and anticipatory guidance regarding challenges to optimistic hopes. As parents reported decision making before IC, interventions prior to IC may be most effective. Further studies are needed to identify predictors of inappropriately high expectations in DBMD clinical trials.

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P.2.16
Cooperative International Neuromuscular Research Group (CINRG) study of echocardiographic outcome measures for use in clinical trials in muscular dystrophy
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Cardiomyopathy is a significant clinical outcome for muscular dystrophy. Echocardiography (echo) is a versatile measure of cardiac function that is available in most muscular dystrophy centers and, therefore, has high utility for clinical care and multicenter clinical trials. Echo outcomes for treatment trials in muscular dystrophy have traditionally measured ejection fraction (EF). However, this measure can be challenging to obtain with more advanced disease due to chest wall deformities and difficulty with positioning for testing. This study was performed to pilot prospective measures of echo outcomes at 5 centers of the Cooperative International