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 prevalent 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-responsive 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 MLA 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
P.2.17
Hypertrophic cardiomyopathy in a patient with Duchenne muscular dystrophy
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Dilated cardiomyopathy is observed in Duchenne muscular dystrophy (DMD). We report the case of a 28 year old DMD patient who exhibited a hypertrophic phenotype and preservation of cardiac function. On cardiac magnetic resonance imaging (CMR), the patient demonstrated severe asymmetric septal hypertrophy, raising the possibility of an underlying genetic cause distinct from DMD. Left ventricular systolic function was preserved with a normal ejection fraction. Additional CMR late gadolinium enhancement (LGE) imaging for myocardial fibrosis demonstrated an unusual LGE pattern. The sub-epicardial LGE in the left ventricular free wall was typical of those found in DMD patients. However, LGE was also present at the right and left ventricular insertion points typical of patients with hypertrophic cardiomyopathy. The patient has a commonly found DMD mutation, duplication in exons 3–4 of the dystrophin gene, predictive of the characteristic DMD dilated cardiomyopathy. Further genetic testing for genes known to cause hypertrophic cardiomyopathy identified two mutations: a heterozygous Glu542Gln mutation in the MYBPC3 gene and a heterozygous Glu1955Lys mutation in the TNNT2 gene. Both mutations have been reported as disease causing in individuals with autosomal dominant hypertrophic cardiomyopathy. This case illustrates the co-occurrence of two relatively common genetic conditions: DMD and HCM. We postulate that these confounding gene mutations led to cardiac muscle hypertrophy, preventing the expected development of the typical dilated cardiomyopathy. The downstream pathways by which the cardiac hypertrophy and myocyte disarray resulting from MYBPC3 and TNNT2 mutations might abrogate cardiac dysfunction caused by dystrophinopathy are unknown but have important clinical implications. They may reveal a potential gene-based therapeutic strategy whereby insertion of a pro-hypertrophic gene variant may ameliorate or prevent dilated cardiomyopathy in DMD patient.

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P.2.18
Bone mineral density and bone mineral content as measures of bone health in ambulatory boys with Duchenne Muscular Dystrophy
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Osteoporosis is a major problem in Duchenne Muscular Dystrophy (DMD) due to long term glucocorticoid (GC) therapy and impaired mobility. Dual-energy xray absorptiometry (DXA) assessment of bone health in DMD boys is challenging, as interpretation is affected by height, delayed bone maturation, puberty, and vertebral fractures. Accurate detection and intervention of osteoporosis are important for improving clinical care in DMD. To assess changes in bone mineral density (BMD) and bone mineral content (BMC) by functional status in ambulatory GC-treated DMD boys, Retrospective study of whole body (WB) and lumbar spine (LS) BMD and BMC by DXA in ambulatory GC-treated DMD boys, assessed from 2/2009 to 7/2012. Bisphosphonate-treated boys were excluded. Age-adjusted z-scores (Z) and height-adjusted z-scores (HAZ) were derived using normal values. Generalized linear modeling was used to analyze changes in BMD and BMC by functional status (functional mobility score, FMS1, 2 or 3, by worsening status). 277 ambulant DMD boys were grouped by FMS (mean ages ±SD for FMS1, 2 and 3: 7.6 ± 2.2, 8.3 ± 2.6 and 11.2 ± 2.6 yrs). GC durations for FMS1, 2 and 3 were 2.7 ± 1.7, 2.9 ± 2.1 and 5.3 ± 2.6 yrs. For whole body, BMD-Z, BMC-HAZ, BMC-Z and BMC-HAZ all decreased with worsening FMS (p < 0.05 for FMS1 vs. FMS2). WB BMC was consistently lower than WB BMD for each FMS group. For spine, BMD-Z was similar between FMS groups, but BMC-Z was lower for FMS3 than FMS1 or FMS2 (p < 0.05). LS BMD-HAZ was surprisingly higher for FMS3 than the other groups, but LS BMC-HAZ remained similar between groups. WB bone indices worsened with declining mobility and increased GC duration. BMC was consistently lower than BMD, and spine BMC showed a relative decrease compared to BMD in weaker boys. Our study suggests that BMC may be a more sensitive indicator of bone health in DMD, and should be considered in conjunction with BMD as part of clinical care.

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P.2.19
Long term growth hormone therapy in Duchenne Muscular Dystrophy (DMD): A case report
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Long term glucocorticoid (GC) treatment compromises linear growth in DMD. Growth hormone (GH) therapy improves height, yet the impact on motor and cardiopulmonary function has not been studied in current DMD research. To report clinical outcomes in a DMD patient on long term GH for GC-induced linear growth failure. Retrospective review of motor, cardiac, and pulmonary outcomes pre- and post-GH therapy. Subject was a 19.6-year-old male with DMD, GC-induced linear growth failure, and GH deficiency (peak stimulated GH of 3.3 ng/mL, normal >10),