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PMO -mediated dystrophin exon 23 skipping restores mitochondrial function in the mdx mouse heart
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Approximately 20% of boys with Duchenne Muscular Dystrophy will die of dilated cardiomyopathy. The cardiomyopathy is characterised by disrupted structure and function of cardiac muscle cells and reduced energy production. However, the mechanisms responsible for the altered energy metabolism have been poorly understood. We have previously sought to identify the mechanisms for metabolic inhibition in mdx mouse cardiomyopathy. Calcium influx through the L-type Ca$^{2+}$ channel (also known as the dihydropyridine receptor) in cardiac myocytes is essential for contraction. Calcium is also important for the regulation of mitochondrial function and production of ATP that is required to meet the energy demands of the heart. We have shown that the L-type Ca$^{2+}$ channel can regulate mitochondrial function and metabolic activity in cardiac myocytes. In mdx heart, the communication between the L-type Ca$^{2+}$ channel and the mitochondria is altered as a result of disruption of the cytoskeletal architecture. This contributes to metabolic inhibition in the mdx heart. We demonstrate that treatment of mdx mice with a phosphorodiamidate morpholino oligomer, designed to induce skipping of dystrophin exon 23, “restored” the increase in mitochondrial membrane potential in mdx cardiomyocytes after activation of the L-type Ca$^{2+}$ channel with the dihydropyridine receptor agonist BayK (−). These results confirm that metabolic inhibition occurs as a result of the absence of dystrophin, and oligomer therapy may be able to normalise metabolic activity and restore contractility in mdx mouse heart.

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P.11.6

Functional motor changes in Duchenne Muscular Dystrophy (DMD) patients on long term daily glucocorticoid (GC) treatment
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Longitudinal review of motor outcomes for a cohort of DMD patients on GC would offer insight into the altered natural history of DMD, provide anticipatory guidance for care management and inform the study designs of future clinical trials. To report the motor outcomes of a cohort of DMD patients on long term daily GC.

Longitudinal retrospective review of timed function tests (TFT) – Timed Gower maneuver (G) (i.e. sit to stand C of pelvis girdle weakness), 10 m walk/run (W/R), North Star Ambulatory Assessment (NSAA); and lower extremity contractures. 110 males aged 7 to ≤13 y were treated with daily GC for 4.8 ± 1.5 y and followed at our clinic for 4.8 ± 1.6 y. Slope changes were 9.0 y for G, 8.5 y for W/R and 8.5 y for NSAA. TFTs were highly correlated regardless of time point. Times for G and W/R were correlated at first (r = 0.76) and most recent visit (r = 0.83). Times for G and NSAA scores were correlated at first (r = 0.76) and most recent visit (r = 0.66). W/R times and NSAA scores were strongly correlated at first (r = 0.82) and most recent visit (r = 0.83). Knee contractures (KC) were not observed in ambulatory boys, but ankle contractures (AC) negatively impacted motor function as the disease progressed. Subjects with AC performed worse on all TFTs at most recent visit compared to those without AC. Linear regression analysis suggests motor function declines faster in subjects with AC compared to those without.

Our slope changes for all three TFTs were >7 years (Mazzone, 2011). Given the strong correlation, the easily executed W/R test may be a clinical surrogate for NSAA in a busy clinic. Our results indicate that early intervention for AC may improve motor outcomes and prolong ambulation in DMD boys.

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P.11.7

Prediction equations based on arm measurements may overestimate standing height in Duchenne Muscular Dystrophy (DMD) patients on glucocorticoid (GC) therapy
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Accurate height measurements (HM) are needed for evaluation of growth and nutrition status, calculation of medication doses, glomerular function, pulmonary function tests (PFT) and 6 min walk tests (6MWT). HM is unreliable in patients with inability to stand or joint or spinal deformities. Prediction equations for height based on arm span (AS) and ulnar length measurements have been established in healthy children. To date, there are no similar prediction equations for children with neuromuscular (NM) disorders. (1) To evaluate the bias in predicted height from Gauld’s (2004) equation based on AS (here, bias is defined as observed height minus predicted height); and (2) to correlate AS and segmental arm span (SAS) measurements with standing height (SH) in children with NM disorders. Cross sectional study of 50 males with DMD on GC and 19 males with NM disorders not on GC treatment (Non GC). SH, AS, SAS were measured. Subjects were 69 males with NM disorders with or without GC treatment (GC 0 N = 50, aged 8.8 ± 2.7 y; Non GC – N = 19, aged 8.3 ± 3.0 y). Gauld’s prediction equation based on AS overestimated SH by a mean of 1.68 ± 2.48 cm in GC group (p < .001); but estimated SH with reasonable accuracy in the non GC group (mean bias +0.12 ± 2.17 cm p = 0.81). AS and SAS were highly correlated with SH in both groups (GC – AS & SH, $r^2 = 0.97$; SAS & SH, $r^2 = 0.95$; non-GC – AS & SH, $r^2 = 0.98$; SAS & SH, $r^2 = 0.97$). Our study verified the accuracy of Gauld’s equation based on AS in the non GC group and noted the overestimation of SH in the GC group. GC induced spine compression fractures and linear growth failure may affect SH in children with NM disorders on GC, thereby limiting the use of standard prediction equations for height in this population. Further studies to obtain accurate height prediction equations in NM patients on GC are warranted when accurate PFTs and 6MWTs are integral outcome measures for clinical care and research.

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P.11.8

The impact of deflazacar on upper extremity function in young adults with Duchenne muscular dystrophy
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Corticosteroid treatment has significantly delayed the progression of Duchenne muscular dystrophy (DMD). Once wheelchair dependent, the adolescent relies on upper extremity (UE) function for activities of daily living including feeding, wheelchair mobility, transfers and recreation. The loss of independent feeding is a major milestone and an adjustment
Height predictions using ulna length are inaccurate in glucocorticoid-treated boys with Duchenne Muscular Dystrophy (DMD)

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Height can be difficult to measure accurately in DMD. Height is essential to assess growth, body mass index, nutritional status, body surface area, pulmonary function and bone health, which are fundamental issues in DMD care. Ulna measurement predicts height in healthy children, and has been proposed as a good predictor of height in DMD. Prediction equations have not been validated in DMD boys on glucocorticoid (GC) therapy. To determine if ulna length accurately predicts standing height in GC-treated DMD boys, we hypothesized that ulna-derived height prediction (U-Ht) is valid in DMD. Cross-sectional study of pre-pubertal, ambulatory, GC-treated DMD boys. Standing heights were compared to U-Ht (all measures performed in triplicate and averaged) using the published equation: height (cm) = 4.605U + 1.308A + 28.003 (U = ulna length; cm; A = age, yrs). Equations were also computed using bone ages (BA) interpreted by a single observer. 43 boys, aged 8.7 ± 1.6 yrs (BA 6.9 ± 1.4 yrs); had received GC for 3.0 ± 1.4 yrs. U-Ht was greater than actual height by 3.4 ± 2.9 cm (p < 0.0001). Height was over-predicted in 91% (39/43) boys (p < 0.0001, Sign test). When age was replaced with BA, this difference decreased: U-Ht using BA was greater than actual height by 0.9 ± 2.6 cm (p = 0.02), and height was over-predicted in 63% (p = 0.1). Using our subjects, we modified the original equation to account for BA delay: height = 4.605U + 1.308A + 28.003 – (1.75 x BA delay). Using age alone, we predicted height as: height = 4.2U + A + 34 (r² = 0.9). U-Ht over-estimates and does not accurately predict height in GC-treated DMD boys. U-Ht predicts height better if BA is used instead of age. GC causes delayed bone maturation and growth failure, resulting in low height age which is closer to BA than actual age, and subject bias with the current age-based equation. U-Ht needs to account for these factors before application in DMD.

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P.11.9
Analyses of 70 patients with Duchenne muscular dystrophy receiving intermittent intravenous combined with oral glucocorticoid therapy

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To investigate retrospectively the clinical and laboratory appearance of Duchenne muscular dystrophy (DMD) and evaluate intermittent intravenous combined with oral glucocorticoid therapy efficacy of glucocorticosteroid.

We collected the clinical, laboratory and follow-up data of 70 patients with DMD who receiving intermittent intravenous combined with oral glucocorticoid therapy, compared the level of serum creatine kinase (CK) and motor ability after glucocorticosteroid therapy with those before glucocorticosteroid therapy by statistical analysis, quantitatively evaluated their myocardium impairments and muscle involvement of lower limb.

1. The level of serum CK had three peaks at the age of 3, 5 and 8 respectively, and significantly decreased after 10–15 days dexamethasone (5–10 mg) intravenous drop infusion, and increased again after 1 month’s prednisone (0.5–0.75 mg/kg/d) oral administration.

2. The motor ability improved in the patients receiving intermittently intravenous dexamethasone.

3. The myocardial perfusion imaging of DMD showed significantly uneven ventricular radionuclide distribution, was “spotted like” change. Intermittently intravenous glucocorticoid therapy had an important effect on improving myocardial perfusion, without significant changes in the heart function.

4. The selective muscle involvement was observed in lower limb MRI, muscles in thigh were more severe than in lower leg, quadriceps femoris and calf were predominantly involved, gracilis and semitendinosus were relatively preserved.

There are hyperCKemia and myocardial damage in the sub-clinical stage of DMD. Myocardium and muscular impairments are positively correlated with age. Intermittent intravenous combined with oral glucocorticoid therapy has an important effect on the protection of motor and cardiac function.

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P.11.11
Pulmonary function characteristics of boys with Duchenne Muscular Dystrophy by age groups, ambulatory status and steroid use

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The lack of natural history data and well-characterized outcome measures limits the ability to conduct therapeutic clinical trials in Duchenne