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Neurobehavioural disorders in Duchenne Muscular Dystrophy

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Variable neurobehavioural disorders and IQ one SD below average are recognised comorbidities in Duchenne muscular dystrophy (DMD), reflecting the disrupted expression of different length dystrophin isoforms in the brain, based on the dystrophin gene mutation site. Following a screening of 84 DMD boys with validated questionnaires, we previously reported 15 with severe learning disability and 41 with scores predictive of autistic spectrum disorder (ASD). Attention deficit and hyperactivity disorder (ADHD) traits, conduct and emotional problems were also described. Overall, a higher proportion of boys affected had mutations towards the 3’end of dystrophin. We performed targeted neuropsychological assessments including: Wechsler Intelligence Children Scale-IV (WISC-IV), Developmental Dimensional and Diagnostic Interview (3Di), Conners-3 Questionnaires, Child Behaviour Checklist (CBCL).

We found marked unevenness of performance on the WISC-IV. Eight out of 12 boys had significant difference between verbal comprehension (VCI) and perceptual reasoning (PRI), with VCI more compromised. Eight out of 19 met criteria for ASD on the 3Di. In 5 boys with ASD the CBCL showed higher scores for internalising and externalising difficulties compared to non-ASD. There were associations between lower IQ and autistic social communication difficulties. On the Conners 6/17 boys met criteria for hyperactivity and 7 for inattention problems. There was a strong association between ASD and severe ADHD symptoms of hyperactivity (OR = 22.5) and inattention (OR = 54). There was a trend towards children with mutations towards the 3’end of the gene, having a greater chance of ASD (OR = 3.4). In our ongoing study, neurobehavioural disorders emerged as important facets in DMD, with confirmed ASD prevalence rates much higher than the general population. Whilst further exploring the role of dystrophin in the brain, children with DMD should be provided with neurobehavioural-targeted support.

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S.P.61

Recurrent pseudo-obstruction and sigmoid volvulus in Duchenne Muscular Dystrophy: A case report

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Dystrophin is expressed in the smooth muscle of the gastrointestinal tract (GIT). In Duchenne Muscular Dystrophy (DMD) a disruption of protein expression can lead to functional disturbances of the GIT including acute gastric dilatation, gasparaesis and intestinal pseudo-obstruction. We report a case of a 24 year old young man with DMD confirmed by a nonsense mutation of intron 44, who developed sigmoid volvulus requiring multiple surgical interventions. Our patient presented with a long-standing history of abdominal bloating and constipation. These episodes, which were initially attributed to the use of night-time BiPAP, progressed into acute abdominal distension with visible large loop of bowels and peristalsis. He had no preceding history of vomiting or abdominal pain. Abdominal radiographic showed a dilated sigmoid colon with features suggestive of volvulus. He had recurrent episodes of pseudo-obstruction over the course of two months, requiring several emergency sigmoidoscopy procedures to decompress obstructed bowel. An abdominal CT scan with contrast confirmed significant paracolic dilatation with volvulus. A definitive procedure was deemed necessary and he underwent subtotal colectomy with ileostomy and gastrostomy insertion. One week later he developed acute gastric necrosis, requiring total gastrectomy and oesophago-jejunosutomy. His post-operative course was aggravated by a peritonitis necessitating a third emergency laparotomy with drainage of the peritoneum. Post-operatively he remained in ICU fully ventilated with a tracheostomy in situ and total parenteral nutrition. Echocardiography showed a moderately impaired systolic function. Our case illustrates that GIT functional disturbances may be serious sequelae in DMD. Non-invasive ventilation and use of steroids can be confounders for underlying GIT dysmotility. Young adults with DMD, who present with...
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Ocular characteristics of Duchenne Muscular Dystrophy
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Electroretinogram (ERG) abnormalities have been described in Duchenne Muscular Dystrophy (DMD). Short isoforms of dystrophin are highly expressed in retina. We sought to expand the retinal phenotypes due to steroid use. 'Negative' scotopic ERGs with reduced a:b-wave amplitude ratios were recorded in all patients with mutations involving exons 44–57, seven patients exons 44–57, affect- ing Dp427 and Dp260, and three patients at the 3' end, in exon 70, affect- ing expression of Dp427, Dp260 and Dp71. Visual acuity, colour vision, intra-ocular pressure measures (IOP) and full field ganzfeld flash ISCEV Electroretinograms (ERGs) were assessed. Patients had normal visual acuity, one boy had a red-green colour vision defect, and two had raised IOP due to steroid use. ‘Negative’ scotopic ERGs with reduced a:b-wave amplitude ratios were recorded in all patients with mutations involving exons 44–57, one patient with a 8–13 deletion and two patients with the 3' mutation involving exon 70. The scotopic oscillatory potential (OP2) was reduced in all boys with mutations of exons 44–57, and in one with 8–13. The photopic OP2 was reduced in patients with deletions upstream of exon 30, but preserved in those patients in whom scotopic OP2 was attenuated. Photopic a:b-wave amplitude ratios were reduced across the cohort, including those with 5' mutations in whom scotopic a:b ratios had been normal. These data show a strong association of mutations downstream of exon 30, the promoter region for Dp260, with abnormal scotopic ERGs. In contrast photopic ERG abnormalities were widespread across all genotypes which may relate to the greater proportion of Dp427, compared with other isoforms, at the synapse of cones to cone on-bipolar cells. Our clinical evaluation also reminds us to monitor IOP during GC treatment.

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Renal dysfunction is a frequent complication in patients with advanced stage of Duchenne muscular dystrophy
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Mechanical ventilation and cardioprotective therapy have significantly improved the prognosis and quality of life of patients with Duchenne muscular dystrophy (DMD). The incidence of congestive heart failure is on declining trend by meticulous care. Meanwhile, elongation of decreased cardiac function can provoke instability in circulation. Recently, we experienced six DMD patients who died from acute renal failure with preserved cardiac function (brain natriuretic peptide: BNP < 100 pg/ml, fractional shortening: FS > 15% and left ventricular diameter: LVD < 50 mm). In some patients, hypovolemia induced by low water intake, diarrhea or dose-up of diuretics was thought to be a trigger of renal failure. Since the value of creatinine (Crnn) decreased in amyotrophic patients, we evaluated renal function in 103 patients with DMD using cystatin C (CysC), which is a sensitive renal marker and unaffected by muscle volume. In addition, we assessed β2-microglobulin (β2MG) in 24 patients, because it is also unaffected by muscle volume. The correlation between logarithm of CysC (LogCysC) and logarithm of b2MG was quite high (r = 0.954), though that between LogCysC and logarithm of Crnn was not adequate (r = 0.623). The average of CysC increased along with age, and more than 30% of patients over 30 years old showed abnormal values. Hemoglobin and logCysC was also negatively associated (r = −0.519), and patients with hemoglobin less than 10 g/dl showed elevated values of CysC. Cardiac indices such as FS (r = −0.250) and logarithm of BNP (r = 0.319) showed weak correlations with logCysC, though significant correlation was not detected between LVD and LogCysC. Since renal dysfunction is a common complication in advanced stage of DMD patients, proper managements of water balance and anemia is important. In the medical managements for DMD, we should pay attention to cardiac–renal–ane- mia association.

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S.P.65
Immunogenicity of intramuscular versus subcutaneous administration of Trivalent Inactivated Influenza Vaccine (TIV) in individuals with neuromuscular diseases

A novel wedged AFO footwear combination (NAFOFC) to improve gait stability was assessed in 10 DMD boys. Primary outcome measure was gait analysis. At visit 1 the boys were cast for the NAFOFC, assessments included: muscle strength, Hammersmith Assessment of Motor Ability (HAMA) and contractures, the 'Activity Scale for Kids' (ASK); and issued an activity logger (activPAL) to use daily for six weeks. At visit 2 NAFOFCs were fitted, the activPAL was re-issued for 6 weeks, and gait was videoed. At 12 weeks (visit 3), boys completed a gait analysis, the ASK and a user satis- faction questionnaire. Preliminary results have been collected for 8 boys: four were household walkers and four community walkers. Time 10 m walks ranged from 7 to 20 s. HAMA scores ranged from 8 to 35. Boys with HAMA <30, fixed hip and knee flexion contractures or fixed ankle equinus >5% were not able to use the NAFOFC successfully. Six out of eight boys completed the data collection: independence (ASK scores) improved for four boys. Only one boy showed improvements in activPAL data: an increase in hours/day spent standing of 6%, and stepping 2%. Five boys found the NAFOFC to be comfortable, four were happy to use them, but only three found them useful. Boys reported NAFOFC to be too heavy, cosmetically unacceptable or walking felt less stable: these boys were more affected by weakness, contractures, and walked less. For NAFOFC to be acceptable and increase participation boys must be community walkers or be independent household walkers who are struggling to maintain their level of mobility. NAFOFC in DMD might improve ambulation in some boys if used at the correct stage of disease progression.

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