P1.15

Left ventricular torsion analysis in Duchenne Muscular Dystrophy

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Cardiac involvement in Duchenne Muscular Dystrophy (DMD) is variable and may develop early in the disease. It is characterized by progressive myocardial fibrosis, myocite atrophy and hypertrophy. Traditional echocardiographic studies can detect changes in the shortening and ejection fraction. We aimed to assess left ventricular torsion (LVT) pattern in DMD/DMB patients who underwent routine echochardiographic controls in our hospital. LVT was evaluated by speckle tracking method using a Vivid 7 machine (Ge Healthcare, Milwaukee, WI). Three left ventricle (LV) short axis images at the basal, mid-ventricular and apical levels were acquired. For off-line analysis, commercially available software (Echo Pac PC 7.0) was used. Images were acquired with an MS3 probe at 90–120 frames/s. Eleven DMD patients, age $13.3 + 6.9$ years old (range 4–27 y/o) were studied. Peak LVT was found to be significantly altered in 6 (54,5%) of them when matched with normal patients of same age and gender obtained from data bases in previous publications. Two of them were found to have isolated LV non-compaction. The rest of the standard echochardiographic parameters included LV ejection fraction were, otherwise, in normal ranges. LVT study by speckle tracking echochardiography gives additional information to the conventional echochardiography assessment, revealing LV affection before cardiac failure symptoms and/ or routine echocardiographic changes arise. This measurement is a new potential tool that could be used in clinical practice as well as in clinical trials to asses the effects of new drugs in DMD cardiomyopathy.

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P1.16

The heart in Duchenne muscular dystrophy: The Cincinnati experience

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Cardiac manifestations of Duchenne muscular dystrophy (DMD) are important but assessment is challenging. Poor acoustic windows in older patients limit utility of transthoracic echocardiography (TTE). While cardiac magnetic resonance imaging (CMR) overcomes this TTE limitation, global cardiac dysfunction, characterized by reduced ejection fraction (EF), is not detected by any imaging modality until disease is advanced. However, CMR myocardial strain (εcc, deformation of an object normalized to its original shape) analysis demonstrates regional cardiac dysfunction in patients of all ages. The purpose of this study is to characterize our DMD-associated cardiac disease CMR experience. CMR studies performed from 2004 to 2011 were analyzed. Standard imaging sequences included cine images, tagged images and myocardial delayed enhancement (MDE). Global ventricular function was assessed using QMASS® and regional function (εcc) by HARP® software; MDE was assessed qualitatively. We analyzed 554 CMR studies from 265 DMD patients and 84 control subjects. Single (105 patients) and serial studies (160 patients) were performed. All patients were >5 years of age, eliminating the need for sedation. Analysis of εcc showed lower magnitude in DMD patients (−12.2 vs. −18.2, $p < 0.0001$) compared to controls despite similar EF (59% vs. 61%, $p = 0.1$). Analysis of serial studies showed that EF changed by only 1.5% (61.8–60.8) while εcc changed by 8.5% (−13.1 to −12.0) over 12 months. The likelihood of positive MDE was greater when EF was abnormal vs. normal (39% vs. 13%, $p < 0.001$). CMR is valuable for assessing DMD associated cardiac disease. While EF manifests global dysfunction late in disease, εcc was abnormal in all DMD patients and εcc magnitude declines with disease progression. The presence of MDE indicates advanced disease with reduced EF. Thus, CMR provides a useful way to characterize DMD associated heart disease at all ages.

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P1.17

A longitudinal analysis of cause-of-death in patients with Duchenne muscular dystrophy in Toneyama National Hospital

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Mechanical ventilation and cardiac protective therapy have improved the prognosis and QOL of the patients with Duchenne muscular dystrophy (DMD). In order to how the introduction of these therapies changes prognosis, we made an analysis of cause-of-death in DMD patients from 1984, when we initiated mechanical ventilation for them. Mean age at death from 1984 to 1993 (1st term, *n*: 49) was 20.0 ± 4.5, from 1994 to 2003 (2nd term, *n*: 48) was 25.2 ± 4.6 and from 2004 to 2010 (3rd term, *n*: 47) was 31.1 ± 5.4, respectively. Because mechanical ventilation was performed by tracheostomy in initial stage, some patients were reluctant to it and as a result respiratory failure occupied 43% of death in 1st term. Patients became acceptable for non-invasive ventilation and home mechanical ventilation (HMV) which were disseminated in 1990s. Consequently, no patients have been died from respiratory failure since 2000. Respiratory physiotherapy and infection control became more important, because many patients receive decades of respiratory managements. Risk management for outpatients also became a serious problem, because the number of in-home sudden-death is increasing along with dissemination of HMV. Cardiac treatments have been performed mainly by diuretics and digitalis in 1st term, angiotensin-converting enzyme inhibitor (ACEI) in 2nd term and combination of ACEI and beta blocker in 3rd term. When comparing to the 2nd term, the frequency of severe cardiac dysfunction (fractional shortening <10%, left ventricle diastolic dimension >75 mm, brain natriuretic peptide >1000 pg/ml) reduced in the 3rd term. In 3rd term, 14% of patients died from renal failure due to circulatory impairment nevertheless their cardiac indices kept mild abnormalities or normal values. We should pay enough attention for cardio-renal-anemia association. Optimized conventional therapies are actually effective however additional innovative therapies are required to further improvement of their clinical course.

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MANIFESTING CARRIERS: POSTER PRESENTATIONS

P1.18

Dystrophinopathy in manifesting female carriers: Clinical and genetic characterization in a cohort of 20 patients

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Mutations in DMD gene lead to Duchenne muscular dystrophy (DMD), milder Becker muscular dystrophy (BMD) and rare X-linked dilated cardiomyopathy (XL-DCM). Female carriers are mainly asymptomatic but 2.5–8% manifests some degree of disease including severe to moderate muscle weakness, mental retardation, exercise intolerance and fatigability, cardiac abnormalities and myalgia. We identified DMD mutations in 20 manifesting carriers (MC), ten of them with no family history of DMD/BMD affected males. We report findings concerning clinical presentation, dystrophin immunostaining, gene mutation and X-inactivation pattern in blood or muscle. The disease onset was in 45% of cases at childhood and P55% at adult age. Main symptoms were severe to mild muscle weakness (65%), myalgia (20%), isolated cardiomyopathy (10%), mental retardation (30%), and exercise intolerance and fatigability (10%). Some patients presented more than one symptom. DMD mutations included 10 exonic deletion (50%), 3 exonic duplication (15%) and 7 point mutations (35%). The majority of patients carried frameshift or truncating mutations (70%). We have compared the X-inactivation pattern in manifesting and non manifesting female carriers. A skewed X-inactivation pattern was present in 69% of MCs and in 30% of non manifesting carriers. There was no complete correlation between phenotype severity, dystrophin immunostaining expression and degree of X-inactivation.

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P1.19

Whole genetic and protein characterisation in DMD symptomatic female carriers excludes correlation with X-inactivation and transcriptional DMD allele balancing

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We have compared the X-inactivation pattern with the DMD alleles transcriptional balancing in muscle tissue from 7 symptomatic and 11 asymptomatic carriers with fully characterised DMD gene mutations. This analysis revealed a complete lack of correlation between X-inactivation, transcriptional balancing and phenotype. The occurrence of skewed X-inactivation in muscle does not correlate with the symptomatic phenotype and the muscle transcriptional representation of the mutated DMD alleles does not mirror the X-inactivation pattern, suggesting that these two mechanisms are independently regulated. The occurrence of a dystrophinopatic phenotype seems to be confidently related to the global amount of the available dystrophin protein. Our data suggest that the regulation both in trans or in cis of the dystrophin protein production represents an extremely relevant determinant influencing the clinical manifestation of dystrophinopathies. The BIO-NMD grant (EC, 7th FP, proposal 241665; www.bio-nmd.eu, to AF as coordinator), the Parent Project – Italy grant (to AF) are gratefully acknowledged.

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P1.20

Complete X-inactivation of the maternally X-chromosome in a girl with Duchenne muscular dystrophy and severe mental retardation

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Preferential inactivation of the normal X chromosome is relatively common in symptomatic female dystrophinopathies. We present a family with a sporadic case of Duchenne Muscular Dystrophy in a young girl due to a deletion in the dystrophin gene on the paternal X-chromosome and a complete X-inactivation of the maternally transmitted X-chromosome. A two and a half year-old Caucasian female, born to healthy, unrelated parents, was referred to the Pediatric Neurology Unit for evaluation of developmental delay. Physical examination revealed motor clumsiness, proximal muscle weakness and impairment of both comprehensive and expressive language. Serum CK levels were above 20,000 UI/L, EMG studies revealed a myopathic pattern, and the muscle biopsy, performed at three years of age, revealed diffuse muscle necrosis mostly involving isolated fibers. Immunohistochemistry and western blotting analysis showed a complete absence of the dystrophin protein. The karyotype was normal and the DNA analysis revealed a deletion of exon 3 to exon 44 of dystrophin in the paternally inherited X-chromosome. A complete methylation of the maternal X chromosome was detected, the abnormal inactivation being also present in one of the X chromosomes in the mother. Since skewed X inactivation is a relatively common feature of X-linked mental retardation, the present and other previously reported cases raise the possibility that abnormal DNA methylation may determine the clinical phenotype in female dystrophinopathies.

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P1.21

Dystrophinopathy in girls due to X-autosome translocations

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Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), also known as dystrophinopathies, are X-linked recessive, allelic, progressive diseases characterized by skeletal muscular degeneration due to total or partial deficit of dystrophin (DYS). DYS is coded by a gene localized on the short arm of chromosome Xp21.2. Carrier females are usually asymptomatic, as only one functional copy of DMD gene is able to produce enough dystrophin. The symptomatic carrier is a well know condition, characterized by female over 18 years of age, presenting with myalgia, cramps, weakness and/or cardiomyopathy. Young females with symptomatic dystrophinopathy are very rare and few cases are reported. We report on two girls with myopathy where cytogenetic analyses were helpful to define DMD dystrophy. Both patients presented with muscular weakness and serum CK level over 10 times the normal. The molecular tests did not detect defects within the gene. The muscular