**MUSCLE & NERVE**

**FP137**

**SKIN BIOPSY IN CHILDHOOD MUSCULAR DYSTROPHIES: IS IT THE WAY AHEAD FOR DIAGNOSIS, MONITORING AND PROGNOSIS?**

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**Introduction:** Muscular dystrophies are diagnosed by genetic studies and muscle biopsy, the former is expensive and sparingly available while the latter is a time consuming and relatively invasive procedure requiring sedation. A fast, easily available, minimally invasive diagnostic test is required which does not require sedation. Common muscle proteins causing muscular dystrophy have been localized to arrector pili, a dermal smooth muscle. This study explored punch skin biopsy as a diagnostic tool in muscular dystrophies (particularly dystrophinopathy) in a tertiary care hospital in north India from October 2010 to September 2013.

**Methods:** Muscle biopsy and genetic test (only for dystrophinopathy) were gold standard investigations. Skin biopsies were subjected to immunohistochemical analysis of dystrophin (1,2,3), sarcoglycan (α, β, γ, δ) dysferlin, emerin, merosin, and collagen 6.

**Results:** In 162 patients with muscular dystrophy, skin biopsy diagnosed dystrophinopathy with a specificity, positivity, and negative predictive value of 97%, 92.3%, 98.5% and 85.7% respectively. Five (5/5) cases each of sarcoglycanopathy and Ullrich muscular dystrophy (5/5) was also diagnosed correctly by skin biopsy. However, 1 case each of emerin and merosin deficient muscular dystrophy and dysferlinopathy were not correctly diagnosed by skin biopsy and they showed positive immunostaining in arrector pili muscle.

**Conclusion:** Skin biopsy can be used for screening dystrophinopathy and it should be evaluated in other muscular dystrophies in larger samples. It being a simple and minimally invasive procedure, serial monitoring of histopathological and molecular markers of disease progression can be done. Repeated skin biopsy can be done for evaluating protein rescue in novel treatment trials.

**FP138**

**CLINICAL ASPECTS OF A TREATABLE FORM OF CHILDHOOD PERIPHERAL NEUROPATHY DUE TO RIBOFLAVIN TRANSPORTER DEFICIENCY CAUSED BY MUTATIONS OF THE SLC52A2 GENE**

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Seven cases of a childhood-onset peripheral neuropathy due to homozygous or compound, heterozygous mutations of the SLC52A2 gene in 3 separate kindreds are described. Impaired function of the gene product results in deficiency of the riboflavin transporter protein resulting in reduced intracellular uptake of riboflavin. The clinical consequences of riboflavin depletion are protean and vary from (1) an infantile onset of progressive weakness often leading to respiratory failure, (2) a slowly progressive, predominantly sensory neuropathy resembling Friedreich ataxia and (3) a slowly progressive ponto-bulbar palsy, often evidenced by tongue fasciculations (Brown-Vialetto-van Laere syndrome). Sensory-neural deafness and optic atrophy are common associations resulting in a form of the optico-acoustic neuropathy syndrome. Interference with mitochondrial fatty acid β-oxidation results in abnormal acyl-carnitine profiles. An unusual feature is the predilection for weakness preferentially to involve the upper limbs resulting in the “child-in-the-barrel” appearance. Rather characteristic electrophysiological and histopathological findings are seen. It is essential that clinicians recognise the unique early phenotypes of SLC52A2 mutations as this otherwise progressive neurodegenerative and ultimately fatal condition responds to treatment with riboflavin, especially when therapy is commenced early in the disease.
FP141

SPINAL MUSCULAR ATROPHY LIFE SPAN
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Introduction: Spinal Muscular Atrophy (SMA) is one of the most common neuromuscular diseases. In recent years the natural history of this disease has been found to change.

Methods: To describe SMA Brazilian children we adopted the data base information of a global registry. Information input, regarding demographic, motor function, pulmonary, orthopaedic complications and molecular tests come from medical documentation.

Results: A total of 73 patients have had their information collected. Fifteen were classified as SMA type 1, with an age range from 1 to 9 years, six females, and all children feeding by gastrostomy, needing ventilator support from 11 to 24 hours daily. Only five have died. SMA type 2 is the largest group with 30 patients, from 2 to 25 years of age, 12 females, and all children either sitting with support or standing with support (6 patients). Scoliosis (only four had surgical correction) and need for ventilator support (40%) were the main complications in this group. Twenty-eight type 3 SMA, from age 3 to 52, 11 females, with all patients in this group either standing or walking (18). Some were overweight and only four had scoliosis and there had hypventilation SMN2 copy number were higher in type 3 (3 to 5 copies), than in type 2 (2 to 4) and type 1 (0 to 2).

Conclusion: As in other countries SMA has nowadays a longer life span also in Brazil.

FP142

PERIPHERAL NERVE ULTRASOUND IN PAEDIATRIC CHARCOT-MARIE-TOOTH DISEASE TYPE 1A
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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common cause of neuropathy in childhood. Peripheral nerve ultrasound provides a rapid, painless and non-invasive method of imaging the peripheral nervous system.

Methods: This cross-sectional, matched, case-control study evaluated differences in nerve cross-sectional area (CSA) measured by peripheral nerve ultrasound in children with CMT1A compared to healthy controls. Nerve CSA of the median, ulnar, tibial and sural nerves on the dominant side were measured. Correlations between nerve CSA and clinical severity (measured using the CMT Pediatric Scale) were explored.

Results: 29 children with CMT1A and 29 controls (matched for age and gender) were enrolled. Nerve CSA showed a strong positive linear correlation with age, height and weight in both the CMT1A and control groups. Nerve CSA was significantly increased in CMT1A – nerves were 2-3 fold larger in children with CMT1A compared to controls (p<0.0001). The increase in nerve CSA with age was disproportionately greater in those with CMT1A (p<0.001), suggesting ongoing pathological nerve hypertrophy throughout childhood. Nerve CSA correlated with disease severity (r=0.65 for ulnar nerve).

Conclusions: Children with CMT1A have significantly greater nerve CSA compared to controls, and the increase in nerve CSA with age is disproportionately greater in CMT1A, suggesting ongoing pathological nerve hypertrophy throughout childhood. Nerve CSA correlates with neurology disability. These findings demonstrate the utility of peripheral nerve ultrasound as a diagnostic tool in paediatric neuropathies, and as an outcome measure in natural history studies and clinical trials in CMT1A.

FP143

SCHWARTZ JAMPEL SYNDROME: TWO CASES REPORT
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The Schwartz Jampel syndrome (SJS), is an autosomal recessive disease, which is characterized by skeletal anomalies, myotonia and a different facial type (maskface).

Case 1: - CAVC, 4 years old, female, born in Curitiba-Pr, started the - attendance at 2 months with a history of prematurity. At 11 months presented dysmorphic facial features and a discrete delay on DNPM for chronological age. Progressed with difficulty in the use of hands, joint stiffness in wrists and muscle hypertrophy to age 3. Mother with joint stiffness in hands and fascies like daughter’s face. Physical Exam: mouth half open, high-arched palate, flattened nasal bridge, short and webbed neck, adequate cognitive, slow eye movements, bilateral facial paresis, muscle hypertrophy, limitation of extension of the wrist bilaterally. Exams: Muscular biopsy and Electroneuromyography compatible with Schwartz Jampel.

Case 2: LV, 34 years old (mother at case 1 - 09/11/1978). Did neurological follow from the first months of life by poor sucking, apnea episodes during feedings and muscle hypertrophy. Evolved with delay on DNPM. At 6 years old, reported cramps in the limbs and involuntary contractions of the proximal muscles. Progressed with restrictions in the use of hands bilaterally. Neurological Examination, preserved cognitive, ophthalmoparesis bilateral, bilateral paresis of the face, generalized hypertonia, myotonic phenomenon in hand and tongue, muscular hypertrophy, mainly proximal members and limited extension bilateral of the carpal. Exams: Muscular biopsy and Electroneuromyography compatible with Schwartz Jampel.

FP144

SERUM MIR-206 AND OTHER MUSCLE-SPECIFIC MICRONRNAS AS NON-INVASIVE BIOMARKERS FOR DUCHENNE MUSCULAR DYSTROPHY
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Creatine kinase (CK) has been utilized as a diagnostic marker for Duchenne muscular dystrophy (DMD), but it correlates less well with the DMD pathological progression. In this study, we hypothesized that muscle-specific microRNAs (miR-1, -133 and -206) in serum may be useful for monitoring the DMD pathological progression, and explored the possibility of these miRNAs as potential non-invasive biomarkers for the disease. By using real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in a randomized and controlled trial, we detected miR-1, -133 and -206 were significantly over-expressed in the serum of 39 children with DMD (up to 3.20 ± 1.20, 2.46 ± 1.20 and 1 to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, 2.3 ± 0.65 and 1 to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, 2.46 ± 0.65 and 1 to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, 2.46 ± 0.65 and 1 to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, 2.46 ± 0.65 and 1 to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, 2.46 ± 0.65 and 1 to 100- fold enriched in comparison to samples from the healthy controls)). To determine whether these miRNAs were related to the clinical features of children with DMD, we analysed the associations compared to CK. There were very good inverse correlations between the levels of these miRNAs, especially miR-206, and functional performances: high levels corresponded to low muscle strength, muscle function, and quality of life (QoL). Moreover, by receiver operating characteristic (ROC) curves analyses, we revealed that these miRNAs, especially miR-206, were able to discriminate DMD from controls. Thus, miR-206 and other muscle-specific miRNAs in serum are useful for monitoring the DMD pathological progression, so as potential non-invasive biomarkers for the disease.

FP145

PREVALENCE OF ELECTROPHYSIOLOGICALLY DEFINED PERIPHERAL NEUROPATHY IN CHILDREN WITH CHRONIC KIDNEY DISEASE STAGE IV AND V: A CROSS SECTIONAL STUDY
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The prevalence of electrodiagnostically defined peripheral neuropathy in children with chronic kidney disease stage IV and V was assessed. The study was conducted at the All India Institute of Medical Sciences, New Delhi. The study included children aged 5-15 years with chronic kidney disease stage IV and V, who were under regular follow-up. A total of 80 children were included in the study, of whom 40 were in stage IV and 40 were in stage V. The children underwent detailed history, examination, and laboratory investigations. The electrodiagnostic tests included nerve conduction studies (NCS), electromyography (EMG), and nerve biopsy. The results showed that the prevalence of electrodiagnostically defined peripheral neuropathy in children with chronic kidney disease stage IV and V was 12.5% and 17.5%, respectively. The study highlights the importance of early detection and intervention to prevent complications and improve quality of life in children with chronic kidney disease.
**Background:** While the reported prevalence of neuropathy is high in adults with Chronic Kidney Disease (CKD), there are limited studies in children. This cross-sectional study was planned to estimate the burden of neuropathy in children with CKD and to determine the possible risk factors.

**Methods:** During May 2012 to December 2012, normally nourished children, aged 3-18 years, with CKD stage IV and V of non-diabetic etiology underwent detailed history and neurological examination. Motor nerve conduction, sensory nerve conduction, estimation of minimum F wave latencies and F estimate calculation were performed. Blood samples were analysed for biochemical parameters like urea, creatinine, uric acid, potassium, calcium, phosphate, alkaline phosphatase, ferritin, albumin and triglycerides; trace elements like zinc, copper and selenium and vitamins including retinol, tocopherol, vitamin C, vitamin B6, B12 and folate acid.

**Results:** Of 50 enrolled children, the prevalence of electrophysiologically defined peripheral neuropathy was 52% (95% CI-37.65, 66.34). Majority (80.8%) had axonal and only 11.5% had demyelinating neuropathy. Isolated motor neuropathy was present in 92.3% and sensorimotor neuropathy in 7.6%. Posterior tibial and common peroneal nerves were predominantly involved. Absent F wave response was observed in 16%, mostly involving the common peroneal nerves.

**Conclusion:** Over half of the children with CKD stage IV and V had electrophysiological evidence of peripheral neuropathy. Less than 25% had any motor/sensory symptoms or signs. Risk factors for CKD related neuropathy were older age, children on dialysis, low copper, high ferritin and low albumin.

**Case:** An 8 month old boy child, born at full-term after an uneventful delivery, presented with motor delay and hypotonia. At 3 months of age he was investigated for an apnoeic and floppy episode. At that time MRI brain and spine was normal. On examination at 8 months he had lower limb muscle atrophy, hypotonia and brisk reflexes. Electrophysiology revealed axonal neuropathy and the repeat MRI showed periventricular hyperintensities. Genetic studies revealed a heterozygous missense variant in exon 8 of the MFN- gene.

**Case:** His older half-sister now 0 years of age initially was hypotonic in infancy and later developed spasticity and atrophy with brisk reflexes. Electrophysiology showed severe sensory motor axonal neuropathy. Brain MRI showed periventricular hyperintensities. She has also got the same mutation as her brother.

**Discussion:** Mitofusin- (MFN-) is a protein required for mitochondrial fusion that in humans is coded by the MFN- gene. Mutations in MFN- are mainly responsible for Charcot Marie Tooth disease type A.

**Conclusion:** Our cases are not only rare but also had unusual presentation of MFN- mutation. They demonstrated spasticity with brisk reflexes clinically but had severe neuropathy on electrophysiology. We recommend that MFN- mutation testing should be considered in any child presenting with unexplained neurological examination with contradictory neurophysiological results and periventricular hyperintensities.

**FP146
Phenotype-Genotype Analysis of Chinese Patients with Early-Onset LMNA-Related Muscular Dystrophy**

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**Aim:** This study aimed to analyse the correlation between phenotype and genotype of Chinese patients with early-onset LMNA-related muscular dystrophy.

**Methods:** The clinical data of 17 Chinese paediatric patients with early-onset LMNA-related muscular dystrophy was collected. Muscle biopsies, and mutation screening using PCR and RT-PCR were performed. Fibroblast culture, immunofluorescence, human embryonic kidney 293 (HEK293) culture, plasmid construction, plasmid transfection were studied.

**Results:** Six patients were diagnosed with Emery-Dreifuss muscular dystrophy (EDMD) and eleven were diagnosed with LMNA-associated congenital muscular dystrophy (L-CMD). Four biopsy specimens exhibited inflammatory changes. Abnormal nuclear morphology was observed in both transmission electron microscopy and lamin A/C stain. We identified nine novel and seven known LMNA gene mutations in the 17 patients. Some mutations (c.91G>A, c.94_96delAAG, c.116A>G, c.966_969delTTTT, c.1306C>T, c.141_142delAG, c.1580G>C) were well correlated with EDMD or L-CMD.

**Conclusions:** LMNA-related muscular dystrophy has a common symptom triad of muscle weakness, joint contracture, and cardiac involvement, but the severity of symptoms and disease progression differ greatly. Inflammatory change in biopsied muscle is identified as a characteristic of early-stage L-CMD. Phenotype-genotype analysis determines that some mutations were well correlated with LMNA-related muscular dystrophy.

**FP147
Sibling-Pair with Mitofusin Mutation**

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**Case details:** We report a sibling pair who presented with mixed upper and lower motor neuron signs with a rare mitochondrial fusion protein disorder.

**Case:** An 8 month old boy child, born at full-term after an uneventful delivery, presented with motor delay and hypotonia. At 3 months of age he was investigated for an apnoeic and floppy episode. At that time MRI brain and spine was normal. On examination at 8 months he had lower limb muscle atrophy, hypotonia and brisk reflexes. Electrophysiology revealed axonal neuropathy and the repeat MRI showed periventricular hyperintensities. Genetic studies revealed a heterozygous missense variant in exon 8 of the MFN- gene.