MUSCLE & NERVE

FP137

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

Biswaroop Chakrabarty, Sheffali Gulati, Mehar Chand Sharma, Manoj Singh, Madhulika Kabra, Ravindra Mohan Pandey, Chitra Sarkar, Rachana Dubey All India Institute of Medical Sciences, New Delhi

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.[1]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 dystrophinopathywith a sensitivity, specificity, positive 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

Manoj P Menezes & Robert A Ouvrier. Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, New South Wales, Australia

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). Sensorineural 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 acylcarnitine 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.

FP139

ENTEROVIRUS 71 ASSOCIATED LOWER MOTOR NEURON DISEASE IN INFANTS AND CHILDREN

T Kandula[1, 2], HL Teoh[1, 2], I Andrews[1], A Bye[1, 2], MA Farrar[1, 2]. [1]Department of Neurology, Sydney Children's Hospital; [2]School of Women's and Children's Health, University of New South Wales, Australia

Introduction: Enterovirus 71(EV71) causes epidemic disease associated with a wide spectrum of neurological disorders. While poliomyelitis has been almost eradicated, EV71 remains a leading cause of acute flaccid paralysis. The present study examined characteristics of EV71 lower motor neuron (LMN) disease to gain further insight into pathogenesis and natural history.

Methods: Clinical and neuroimaging characteristics together with outcomes were examined in 14 children (age range 0.5-7.8 years, mean 2.1±0.5 years) with proven EV71 infection and acute flaccid paralysis or motor cranial nerve palsy from two epidemics in 2000 and 2013.

Results: Extent of clinical disease was greater in the earlier epidemic (2000-6/6 patients had bilateral multisegment LMN disease involving brainstem motor nuclei, cervical, thoracic and lumbar segments; 2013-7/8 patients had focal unilateral paresis-3 upper limb, 3 lower limb, 1 cranial nerve, P=0.005). Neuroimaging differed between epidemics (2000-MRI demonstrated T2-hyperintense lesions in spinal cord/brainstem motor nuclei in 6 patients; 2013-no signal changes demonstrated in motor nuclei, P=0.001). 6/6 patients from 2000 had long-term residual weakness and 3/6(50%) required long term ventilation. While the natural history of recent patients is emerging, 3/8 recovered fully (median follow-up 6 months) and no patient remains ventilated.

Conclusion: Focal EV71 disease of LMNs occurs throughout the brainstem and spinal cord, and like polio, often results in permanent paralysis. Outcome may be related to extent of initial disease, neuroimaging involvement of motor nuclei/anterior horn cells and specific epidemic. Differences between epidemics in clinical, neuroimaging and natural history of EV71 LMN disease may relate to subtype and virulence.

FP140

BONE HEALTH IN DUCHENNE MUSCULAR DYSTROPHY: NATURAL HISTORY, PATHOGENESIS AND TREATMENT

Hugo Sampaio, Sydney Children's Hospital, Australia

Introduction: Duchenne muscular dystrophy (DMD) patients are vulnerable to osteoporosis and fractures. The present study examined the natural history and determinants of bone health in DMD to gain further insight into pathogenesis and guide future treatment strategies.

Methods: Fracture pattern, ambulation status, chronic corticosteroid therapy, vitamin D (25-OHD) levels and body mass index (BMI) were retrospectively analysed in 48 DMD patients. The Kaplan-Meier method was used to obtain fracture probabilities. Cross-sectional analysis of Vitamin D was performed in 31 DMD patients and related to treatment.

Results: 43% of DMD patients had ≥1 fracture. Fracture probabilities at ages 6, 9, 12 and 15 years were 4%, 9%, 31% and 60% respectively, accelerating around the time of ambulation loss (11.8 ± 2.7 years). Overweight or obese patients had greater fracture rate than those with normal BMI (61% and 11% respectively, P<0.05). Chronic corticosteroid therapy was utilised in 69%. A history of 25-OHD deficiency occurred in 84% and current deficiency was present in 35% of patients. Despite chronic 25-OHD supplementation, 8/21 (38%) of current patients were deficient.

Conclusions: The natural history of fracture in DMD confirms that osteoporosis and pathological fracture remain a major concern, with multiple risk factors. The present study highlights the importance of instituting a multidisciplinary approach optimising bone health at the time of diagnosis of DMD and prior to loss of ambulation. This includes regular vitamin D supplementation, weight-bearing exercise and dietary education. The optimum dose of vitamin D and safety and utility of prophylactic bisphophonates warrant further study.

FP141

SPINAL MUSCULAR ATROPHY LIFE SPAN

Alexandra Prufer de Q. C. Araujo, Giuseppe Mario Carmine Pastura, Marlos Melo Martins, Aline Chacon Pereira, Roberta da Silva Mendonça Thurler, Sheyla Ribeiro Magalhães, Alessandra Maria Rocha Rodrigues, Rita Farias de Oliveira, Karen Grazielle Capuano de Sant'Anna, Viviane Romão Soares da Rocha. The Federal University of Rio de Janeiro (UFRJ), Brazil

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 three had hypoventilation. 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

EppieYiu[1, 2, 3], Cain Brockley[4], Katherine Lee[5], Kate Carroll[1], Katy De Valle[1], Rachel Kennedy[1], Padma Rao[4], Monique Ryan[1]. [1]Neurology Department, Royal Children's Hospital Melbourne, Australia; [2]Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Australia; [3]Department of Paediatrics, The University of Melbourne, Australia; [4]Radiology Department, Royal Children's Hospital Melbourne, Australia; [5]Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute,, Australia

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 ($p<0.001$). 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 ($r=0.63$ 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

Joao Francisco Tussolini[1], Isac Bruck[2], Sergio Antonio Antoniuk[3], Lucia Helena Coutinho Dos Santos[3], Danielle Caldas Bufara Rodrigues[3], Ana Cristina Crippa[3], Paula Vilar[3], Alcir Francisco Silva[3]. [1]Hospital De Clinicas - Universidade Federal Do Paraná, Brazil; [2]neurologia Ufpr, Brazil; [3]UFPR, Brazil

The Schwartz Jampel syndrome (SJS), is an autosomal recessive disease, which is characterized by skeletal anomalies, myotonias 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 MICRORNAS AS NON-INVASIVE BIOMARKERS FOR DUCHENNE MUSCULAR DYSTROPHY

Jun Hu. Children's Hospital, Chongqing Medical University, China

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, $2^{-\Delta\Delta Ct}$): almost 10- to 100- fold enriched in comparison to samples from the healthy controls (less than 1.15 ± 0.34, $2^{-\Delta\Delta Ct}$). 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

Sangeetha Yoganathan, Sheffali Gulati, Arvind Bagga, Gs Toteja, Pankaj Hari, Aditi Sinha, Ravindra Manohar Pandey, Mohammad Irshad. All India Institute Of Medical Sciences, India

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 B_{12} and folic 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.

FP146

PHENOTYPE–GENOTYPE ANALYSIS OF CHINESE PATIENTS WITH EARLY-ONSET LMNA-RELATED MUSCULAR DYSTROPHY

Hui Xiong. Department of Pediatrics, Peking University First Hospital, China

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 (HEK 293) 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.745C>T, c.746G>A, and 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

Siddharth Jain, Tracy Willis, Evangeline Wassmer, Shakti Agrawal.Birmingham Children's Hospital, United Kingdom

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.

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.

FP148

DE NOVO GAIN-OF-FUNCTION MUTATION IN SCN11A: NO PAIN, MORE PAIN, OR A BIT OF BOTH?

Mohamed Osman Eltahir Babiker[1], Iain Horrocks[1], John Tolmie[2], Catherine McWilliam[3], Paula Beattie[4], Juliet Tucker[5], Christopher Geoff Woods[6]. [1]Fraser of Allander Neurosciences Unit, Royal Hopsital for Sick Children, Glasgow, United Kingdom, United Kingdom; [2]Department of Clinical Genetics, Southern General Hospital, Glasgow, UK, —; [3]Human Genetics Unit, Ninewells Hospital, Dundee, UK, United Kingdom; [4]Dermatology Department, Royal Hospital for Sick Children, Glasgow, UK., United Kingdom; [5]Women`s & Children Service, Forth Valley Royal Hospital, Larbert, UK, United Kingdom; [6]Department of Clinical Genetics, ATC, Addenbrooke's Hospital, Cambridge, UK, United Kingdom

Background: The genotypic and phenotypic spectrum of pain-related channelopathies is expanding. Various mutations in the genes encoding voltage-gated sodium channels have been identified. This is best exemplified in ***SCN9A*** gene mutations whereby loss-of-function mutations lead to indifference to pain. Conversely, gain-of-function mutations result in paroxysmal extreme pain disorder and primary erythermalgia. Recently, Leipold et al. (2013) reported 2 cases of congenital insensitivity to pain due to a de novo gain-of-function mutation in ***SCN11A.*** Clinically, patients had universal loss of pain perception and self-inflicted injuries.

Aim: To describe a case with a similar ***SCN11A*** mutation in whom a mixed picture of pain insensitivity and episodic visceral pain predominates.

Case report: This 6-year-old girl had a history of chronic diarrhoea and failure to thrive during the first year of life. Difficult-to-heal wounds were noted. Moreover, she had mouth ulcers that were self-inflicted by biting. Cognitive development was normal. Motor development was slightly delayed with generalized hypotonia and weakness. She then started to have abdominal pain made worse by defecation and urination. Other symptoms were excessive sweating, persistent pruritus and cold intolerance. A de novo heterozygous mutation in ***SCN11A*** which encodes one of the sodium channels ($Na_v1.9$) was found. This was a p.Leu811Pro missense gain-of-function mutation.

Discussion & Conclusion: This case expands the phenotype of a novel mutation in a gene encoding a voltage-gated sodium channel. Mutational analysis of ***SCN11A*** gene in similar cases is recommended. Studies to increase understanding of pain pathways and targeted treatments are needed.