O.8 Characterization of Japanese patients with myofibrillar myopathy

Myofibrillar myopathy (MFM) is a group of genetically heterogeneous disorders characterized by protein aggregates in muscle fibers associated with markedly disorganized myofilaments. To date, 7 causative genes were identified including DES, CRYAB, ZASP, MYOT, FLNC, BAG3, and FHHL1. To know the character of Japanese patients with MFM, we performed mutation screening in 114 Japanese patients with MFM. Clinical and pathological findings were analyzed. In our series, number of patients with mutations in DES, ZASP, MYOT, FLNC, BAG3, and FHHL1 were 6, 6, 4, 6, 2, and 6, respectively. No patient with CRYAB mutation was identified. Clinical and pathological characterization of these patients was performed. We further screened VCP mutation and identified 5 patients in our series. One patient show cerebellar signs, but the remaining four patients show no clinical symptoms for Paget’s disease of bone and front-temporal dementia. From the pathological points of view, VCP could also include a causative gene for MFM. Clinical features of MFM patients are quite variable. Frequency of each causative gene was different from the previous reports. In our series, no mutation was identified in 69% of the MFM patients. Additional responsible genes should be identified.

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SMA CLINICAL: POSTER PRESENTATIONS

P3.1 Brown–Vialetto–Van Laere and Fazio Londe overlap syndromes: A clinical, biochemical and genetic study in 6 patients

Units of Neuromuscular Disorders, Rehabilitation and Laboratory of Biochemistry, Bambino Gesu’ Children’s Research Hospital, Rome, Italy; C. Besta Institute, Milano, Italy

Brown–Vialetto–van Laere (BVV) and Fazio Londe (FL) syndromes are rare neuromuscular disorders affecting motor neurons. BVV is associated with deafness while FL is not, but both have a progressive ponto-bulbar palsy with associated severe respiratory involvement. One gene C20orf54 of BVV has been cloned recently (Green et al., 2010) and another report demonstrated that BVV is related to a defect in riboflavin transport (Bosch et al., 2010). In the last 2 years we recruited 6 patients, 2 girls and 4 boys, with clinical features reminiscent of the BVV&FL overlap syndromes. In patients we measured levels of riboflavin and redox state in blood; motor function was assessed by ALS functional rating scale, and FVC. We also performed electrophysiological studies, collected DNA in all patients, and sequenced the gene C20orf54. Age range of patients: 11–16 years old. Two of these patients started to manifest isolated neurosensory deafness, 1 at age 3 and 1 at age 10 years. Two deaf patients started several years later to manifest subacute progressive ponto-bulbar palsy with dysphonia, dysphagia and respiratory problems. A third patient markedly improved after IVIG, but then relapsed remaining unresponsive to treatment. This patient was not deaf but had abnormal auditory evoked responses (BAERs). The other 3 remaining patients had no deafness; two had subacute progressive ponto-bulbar palsy while the other patient had swallowing difficulties. We found hetero compound mutations in C20orf54 from only 3/6 patients who manifested deafness or abnormal BAERs. Mutated patients had reduced levels of riboflavin in blood. With riboflavin supplementation 10 mg/kg/day the most severely affected patient stopped progression of symptoms in the time scale of 6 month. BVV and FL syndromes are severe progressive motor neuron disease. In patients affected by BVV and mutated in C20orf54 riboflavin supplementation is able to stabilize and improve the severe progression of the disease.

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P3.2 Novel mutation of TRPV4 in congenital distal SMA with vocal cord paralysis

IRCCS Stella Maris, Molecular Medicine and Neuromuscular Disorders, Pisa, Italy; Medical University of Graz, Graz, Austria

Transient receptor potential vanilloid 4 gene (TRPV4) is a cation channel that mediates intracellular calcium influx in response to several stimuli. Recently, mutations in the ankyrin domain of TRPV4 were shown to cause congenital distal spinal muscular atrophy (SMA), scapuloperoneal SMA, and hereditary neuropathy type 2C. We present clinical, molecular, and muscle MRI features of a young girl with congenital distal SMA and vocal cord paralysis in whom we identified a novel TRPV4 mutation. The mutation is unexpectedly localized in amino-terminus domain of the protein. In vitro experiments, including calcium imaging and patch-clamp studies, showed a significant loss-of-function in HeLa cells carrying the human mutation. Expression of TRPV4 protein on muscle tissue and fibroblasts from the patient did not seem to be affected. We also searched for mutations TRPV4 in 4 cases of congenital distal SMA without vocal cord involvement and did not detect any pathological variant. Adding to the molecular heterogeneity of TRPV4-diseases, our results also confirm the selective role of the protein in the pathogenesis of vocal cord paralysis.

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P3.3 Does muscle strength deteriorate over time in Spinal muscular atrophy type II and III? Fifteen years follow up study in 22 patients with SMA II and 9 patients with SMA III
U. Werlauff, J. Vissing, B.F. Steffensen

The Danish National Rehabilitation Center for Neuromuscular Diseases, Aarhus, Denmark; Neuromuscular Clinic and Research Unit, Rigshospitalet, Copenhagen, Denmark

Patients with Spinal muscular atrophy (SMA) types II or III loose physical function over time, but there isn’t agreement on whether muscle strength deteriorates and how to measure it. A cross sectional study showed that older patients with SMA II had weaker muscles and less physical function compared to younger patients indicating loss of muscle strength over time. Change of muscle strength as measured by dynamometry was not found in patients with SMA II and III in two studies over a period of one to six years, other two studies have shown a decline in muscle strength measured by manual muscle test (MMT) in patients with SMA II over ten years and five years respectively. Deterioration of muscle strength measured by MMT was also shown in a study with at least 10 years follow-up in SMA III patients with onset >3 years. The aim of this study is to evaluate muscle strength and physical function over a period of 15 years in patients with genetically and clinically confirmed SMA types II and III. Twenty-two patients with SMA II (median age at entry 14 [7–53]) and nine patients with SMA III (median age at entry 32[12–46] participated. All patients were assessed at the National Center for Neuromuscular Diseases 3–5 times during a period
Spinal muscular atrophy with respiratory distress type 1 (SMARD-1). A clinicopathological follow-up

B. San Millán-Tejado a, S. Teijeira b, J.M. Fernandez b, C. Navarro a

a University Hospital of Vigo, Neuropathology, Vigo, Spain; b University Hospital of Vigo, Neurophysiology, Vigo, Spain

Spinal muscular atrophy with respiratory distress type 1 is a clinically and genetically distinct form of spinal muscular atrophy type 1 that results from irreversible degeneration of alpha-motor neurons in the anterior horns of the spinal cord. A 3 month-old girl presented with neonatal respiratory distress followed by progressive limb weakness and marked generalized hypotonia with areflexia. Despite supportive measures, the baby died of respiratory insufficiency at 23 months of age. Extensive electrophysiological examinations, nerve and muscle biopsies at 5 and 10 months of age, molecular investigations and post mortem studies were performed. Progressive and severe axonal neuropathy, unilateral phrenic paralysis and a generalised neurogenic pattern were found in consecutive electrophysiological examinations. Histochemical studies of nerve and muscle biopsies revealed progression of damage including axonal loss and neurogenic muscle atrophy. Post-mortem studies demonstrated significant neuronal loss of motor neurons in the anterior horns of the spinal cord and a severe axonal depletion in peripheral nerves. Molecular analysis of IGHMBP2 on 11q13-q21 revealed the nonsense mutations R147X and C496X in the patient, from maternal and paternal origin, respectively. This is the first Spanish patient with SMARD1 and one of the very few with post-mortem studies. Early respiratory insufficiency and muscle weakness of unclear cause in children should alert of SMARD1.

IGHMBP2 gene should be sequenced, once SMA gene mutations have been ruled out.

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P3.4

Oxidative defect in a large cohort of genetically-determined SMA cases

A. Berardini 1, G. Fagiolari 2, D. Vallejo 3, V. Lucchi 1, A. Bordoni b, C. Lamperti 1, M. Ripolone 1, S. Corti 1, U. Balottin 1, N. Bresolin 1, G. Comi 1, a, M. Sciaocco b, M. Moggi c

1 Struttura SCNP Fondazione IRCCS C. Mondino, Infantile Neuropsychiatry, Pavia, Italy; 2 Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, University of Milan, U.O. Neurologia, Neurology, Neuromuscular Unit, Milan, Italy; 3 Universidad de Antioquia, SIEN Neurologia, Neurology, Medellin, Colombia; 4 Fondazione IRCCS, Istituto Neuroligico Besta, Neurology, Milan, Italy; 5 Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, University of Milan, U.O. Neurologia, Neurology, Milan, Italy

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutations in the SMN1 gene. Based on age of onset and clinical course, patients can be divided into three main groups (type I, II and III). Severe depletion of mitochondrial DNA is reported in patients with SMA and as a consequence of the severe fiber atrophy. Also, mtDNA depletion was found in patients with TK2 mutations and a SMA-like phenotype. In addition, TK2 null mice showed a COX deficiency in the anterior horn. This prompted us to make a systematic revision of our collection of 20 skeletal muscle samples from genetically-ascertained SMA patients (9 type I, 4 type II and 7 type III patients). Besides routine histological and histochemical reactions, we performed histochemistry for COX, SDH, and combined COX/SDH stains. In all patients, skeletal muscle biopsy showed a chronic neurogenic pattern, with groups of atrophic fibers and fiber type grouping. In addition, variable, but unequivocal COX deficiency was evident in most samples and was very severe in SMA I cases, where the enzyme stain was totally lacking. In all specimens, the enzyme defect was evident in both atrophic and normal/hypertrophic fibers. No histochemical defect was found in healthy control muscles and in muscles from patients with chronic neurogenic disorders. Quantitative mtDNA studies are underway. Our data show that histochemical COX deficiency is a common finding in skeletal muscle from SMA patients. We found a correlation between severity of the oxidative defect, patient age and disease onset/duration. However, there was no correlation between denervation and COX-deficiency based on two main criteria: first, both normal-size and hypertrophic muscle fibers were also COX-deficient in SMA patients; second, no COX deficiency was seen in non-SMA neurogenic atrophy. Our findings support the hypothesis that mitochondrial dysfunction could play a role in the pathogenesis of the disease.

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P3.5

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Progressive and severe axonal neuropathy, unilateral phrenic paralysis and a generalised neurogenic pattern were found in consecutive electrophysiological examinations. Histochemical studies of nerve and muscle biopsies revealed progression of damage including axonal loss and neurogenic muscle atrophy. Post-mortem studies demonstrated significant neuronal loss of motor neurons in the anterior horns of the spinal cord and a severe axonal depletion in peripheral nerves. Molecular analysis of IGHMBP2 on 11q13-q21 revealed the nonsense mutations R147X and C496X in the patient, from maternal and paternal origin, respectively. This is the first Spanish patient with SMARD1 and one of the very few with post-mortem studies. Early respiratory insufficiency and muscle weakness of unclear cause in children should alert of SMARD1. IGHMBP2 gene should be sequenced, once SMA gene mutations have been ruled out.

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P3.6

Segmental distribution of muscle weakness in Dutch patients with SMA type 2, 3 and 4

R.J. Wadman a, L.H. van den Berg b, W.L. van der Pol b

a The Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Neurology, Utrecht, Netherlands; b The Rudolph Magnus Institute for Neuroscience, University Medical Center Utrecht, Neurology, Utrecht, Netherlands

Spinal muscular atrophy (SMA) is characterized by proximal weakness, loss of motor neurons in the anterior horn and homozgyous deletion of the SMN1 gene. Age at onset and acquired motor milestones are used to classify SMA in 4 types. Proximal weakness is described in most studies, but recent studies have suggested that weakness in patients with SMA is segmentally distributed. We investigated patterns of weakness in 52 patients with SMA types 2–4. The Medical Research Council (MRC) Scale was used to document muscle strength in 23 patients with SMA type 2, 15 with type 3a, 12 with type 3b, and 2 with type 4. Muscle strength was measured in 36 different muscle groups, innervated by upper (C5–6; L1-L2), middle (C7-C8; L3-L5) or lower regions (C8-Th1; S1-S2) of the cervical and lumbosacral spinal cord. We used the non-parametric Wilcoxon Signed Rank test for statistical analyses. Fifteen patients were still ambulant at the date of examination. Mean disease duration was 25 years (range 1.5–65 years). The legs were more severely affected than the arms in all patients. Hand function was relatively preserved. Muscle weakness was segmentally distributed. The middle cervical region was significantly more affected than the upper cervical region in all SMA types. Biceps were significantly stronger than triceps in SMA type 2 and 3 of all ages. The middle lumbosacral region was significantly stronger than the upper lumbosacral region in all patients. The iliopsoas were significantly weaker than the adductors in patients with SMA, especially in patients with SMA type 2. All patients with SMA type 2 had areflexia. All deep tendon reflexes were lost in non-ambulant patients with SMA type 3, except for one. The deep tendon reflex of the triceps was more often absent than the biceps reflex. Muscle weakness in SMA is segmentally distributed. Pat-