P2.59
Lumbosacral paravertebral muscle MRI evaluation in dysferlinopathies
A. Matos a, A. Geraldo a, M.A. Portilho b, M. Seco b, C. Marques b, L. Negrão a
a Coimbra’s University Hospital, Neuromuscular Outpatient Department, Coimbra, Portugal; b Coimbra’s University Hospital, Radiology Department, Coimbra, Portugal

Dysferlinopathies are autosomal recessive muscular dystrophies secondary to mutations in the DYSF. Phenoypic expression can vary from assymptomatic HyperCKemias, Miyoshi myopathy, LGMD2B, and other rarer presentations. Recently it has been reported that lumbosacral paravertebral muscles can also be easily affected. To present the lumbosacral paravertebral, pelvic, girdle, thigh and leg muscle MRI and correlate lumbosacral paravertebral muscle findings with clinical findings in adult dysferlinopathy patients. The clinical, pathological and genetic findings of the patients with a dysferlinopathy were analysed. Lumbosacral, pelvic girdle, thigh and leg muscle MRI (1.5 Tesla) was performed. Dysferlinopathy diagnosis was made in 16 patients and MRI evaluation was done in 12. One patient had assymptomatic hyperCKemia, 1 had distal anterior compartment myopathy, 2 a Miyoshi myopathy and 8 a LGMD2B. Parental consanguinity was reported in 7 patients. Their actual mean age is 46.4 years (28–75 years) and the mean age of first symptoms was 29.8 years (16–69 years). The mean time from first symptoms to genetic diagnosis was 11.5 years (3–43 years). Two are wheelchair bound. The mean CK value was 4717 UI/l. Genetic results revealed homozygous mutations in 7 patients, compound heterozygous mutations in 4 patients and a single pathogenic mutation was found in 1 patient. Muscle MRI revealed lumbosacral muscle adipose infiltration in 11 patients, slight in 2 patients and severe in 9. The patient with no lesion of the lumbosacral muscles is a symptomatic patient with a proximo-distal form of disease. One of the patients with slight degeneration of lumbosacral muscles is asymptomatic and the other is pauci-symptomatic. This study shows that lumbosacral muscles are affected in all stages and phenotypes of dysferlinopathy patients. Muscle MRI of the other segments will be helpful to understand its role in muscle tissue.

doi:10.1016/j.nmd.2011.06.880

P2.60
Distal myopathy caused by a homozygous mutation in the titin gene
L. Negrão a, S. Penttila b, A. Matos a, O. Rebelo a, A. Geraldo a, A. Vihola a, P. Hackman b, U. Udd c
a Coimbra University Hospitals, Neurology, Coimbra, Portugal; b University of Tampere, Neuromuscular Research Unit, Tampere, Finland; c University of Helsinki, Medical Genetics, Helsinki, Finland

Muscle disease causing mutations in the titin gene (TTN) were first identified in Finland. They are responsible for two main phenotypes: the AD late onset distal myopathy and the AR early onset limb-girdle muscular dystrophy. We report a Portuguese patient with the clinical phenotype of distal myopathy caused by a homozygous mutation in the TTN gene. The patient is a 26 year old Caucasian female, the only child of a clinically normal first degree consanguineous couple. At the age of 22, she started to complain of weakness in the lower limbs. The patient had atrophy of the tibialis anterior muscles and bilateral weakness of the tibialis anterior (1/5 MRC) and peronei muscles (4/5 MRC) and she walked with a bilateral steppage gait. The Achilles tendon reflexes were abolished. The Gowers’ maneuver was negative. The CK value was moderately elevated. EMG of the tibialis anterior and peroneus longus muscles showed a myopathic pattern. Muscle MRI revealed a marked and symmetrical atrophy and fat infiltration of the legs’ anterolateral compartment muscles and of the soleus muscles. Histological examination of the left deltoid muscle showed signs of a moderate myopathic lesion. Molecular study identified the homozygous mutation g.293376delA (p.K33395NfsX8) in exon 363 of the TTN gene. The first Portuguese patient with muscle disease caused by a TTN gene mutation presented the same mutation reported in distal myopathy patients from Spain and thus represents an Iberian founder mutation. It is also the first time a homozygous C-terminal TTN gene mutation is not associated with the rarer LGMD-phenotype. The reason for the lower penetrance in the parents and the formally recessive type of distal myopathy in the proband is under study using gene and protein expression assays.

doi:10.1016/j.nmd.2011.06.882

HEREDITARY INCLUSION BODY MYOPATHY: POSTER PRESENTATIONS

P2.61
Metabolic changes in sialic acid synthesis pathway in DMRV/hIBM model mice with long-term sialic acid treatment
S. Noguchi, M.C. Malicdan, F. Funato, I. Nishino
National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

Distal myopathy with rimmed vacuoles or hereditary inclusion body myopathy (DMRV/hIBM) is an autosomal recessive disorder characterized by muscle atrophy, weakness that initially involves the distal muscles, and presence of accumulated proteins and rimmed vacuoles in myofibers. DMRV/hIBM is secondary to mutations in the GNE gene, which encodes an essential enzyme in sialic acid biosynthesis. We recently showed that muscle atrophy and weakness were completely prevented in the DMRV/hIBM mouse after treatment with sialic acid (NeuAc and sialyllactose) and its precursor (ManNAc). In a recent report of neonatal suckling rats, the endogenous sialic acid synthesis in colon is either inactivated or activated depending on milk sialic acid level. This finding implies that long-term treatment of DMRV/hIBM patients with sialic acid may affect sialic acid biosynthetic pathway. In this study, we first analysed the expression of genes encoding the enzymes and transporter in sialic acid biosynthesis pathway in various organs of non-treated wild mouse. The genes involved in synthesis are highly expressed in liver, while those involved in degradation are high in kidney, suggesting that liver is an anabolic organ and kidney is a catabolic organ for sialic acid synthesis. We then examined the expression of genes in skeletal muscle, liver and kidney of DMRV/hIBM mouse after long-term treatment with NeuAc and sialyllactose or ManNAc for more than 300 days and found that the genes for catabolic enzymes were further up-regulated in kidney, while the genes for anabolic
P2.62

Expanding clinicopathological findings observed in the Asian patients with VCP mutation

National Institute of Neuroscience, NCNP, Tokyo, Japan

Mutations in the valosin-containing protein (VCP) gene are known to cause inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBM/PFD) and familial amyotrophic lateral sclerosis (ALS). We performed mutation screening of VCP in a total of 151 Asian patients with rimmed vacuolar myopathy. Detailed clinical and pathological analyses were done for the patients with VCP mutation. We identified VCP mutations in five unrelated Japanese and one Korean patients. Five different missense mutations were found including a novel p.Ala439Pro substitution. All patients had adult-onset progressive muscular wasting with variable involvement of axial, proximal, and distal muscles. Only one of 6 patients had mental disorder with cerebellar signs, and none showed radiological changes consistent with Paget's disease of bone (PDB). Muscle cramps, pain, and fasciculation were often seen. Involvement of motor neurons and peripheral nerves was suggested in all the patients from clinical, electrophysiological, and muscle pathological examinations. Scattered cytoplasmic and nuclear inclusions are characterized by mutations in VCP should be considered for adult-onset rimmed vacuolated myopathy with variable neuropathic changes. Low frequency of PDB and wide variety of neuropathic involvement may complicate the diagnosis of this multisystem disorder.

doi:10.1016/j.nmd.2011.06.883

P2.63

Clinical and molecular genetic features of Korean patients with GNE mutations

Y.E. Park a, H.S. Kim b, E.S. Choi c, S.Y. Kim d, D.S. Kim e
a Pusan National University Hospital, Department of Neurology and Medical Research Institute, Busan, Republic of Korea; b Pusan National University Yangsan Hospital, Medical Research Institute, Yangsan, Republic of Korea; c Pusan National University Hospital, Medical Research Institute, Busan, Republic of Korea; d Ulsan University Hospital, Department of Neurology, Ulsan, Republic of Korea; e Pusan National University School of Medicine, Department of Neurology and Medical Research Institute, Yangsan, Republic of Korea

The GNE encodes a bifunctional enzyme, UDP N-acetylgalactosamine 2-epimerase/N-acetylmannosamine kinase, critical for the production of sialic acid. And, it is responsible for development of distal myopathy with rimmed vacuoles and hereditary inclusion body myopathy. These are characterized by late onset, progressive muscular weakness and rimmed vacuoles on muscle pathology. We are to analyze clinical and molecular aspects of Korean patients with GNE mutations. Six patients were included in this study based on progressive limb weakness and GNE mutations, and analyzed for onset age, initial symptoms, distribution of muscle atrophy and disease progression. Muscle pathology was observed by light and electron microscopes. PCR reactions were done with genomic DNA from the patients’ blood leukocytes. PCR products were directly sequenced, and novel mutations were further confirmed by RFLP and comparing with 100 normal controls. All the patients had onset in early adulthood. Initial symptoms were variable with gait disturbance, difficulty climbing, waddling gait and minimal weakness with leg atrophy. One patient characteristically demonstrated posterior thigh muscle atrophy with spared lower leg muscles on CT scan. Muscle pathology from two patients was lack of rimmed vacuoles. We have found six mutations, three of which were novel. The most common mutation was p.Val572Leu with 5/12 allele frequency. Our patients with GNE mutations showed phenotypic heterogeneity; some patients have manifested initially proximal limb muscle weakness, and one patient rapidly progressed to a wheelchair-bound state. In addition, mutational analysis showed ethnic specificity with high allele frequency of p.Val572-Leu, which is totally different from that of Iranian Jewish. Although our study included only limited number of patients, with these results we may characterize clinical and molecular genetic features of Korean patients with GNE mutations.

doi:10.1016/j.nmd.2011.06.884

P2.64

Muscle imaging in hereditary inclusion-body myopathy

G. Tasca a, A. Broccoli b, C. Rodolico b, T. Gidaro b, R. Morosetti b, M. Monforte b, E. Barca a, E. Ricci a, M. Mirabella a
a Catholic University School of Medicine, Department of Neuroscience, Rome, Italy; b University of Messina, Department of Neurosciences, Psychiatry and Anaesthesiology, Messina, Italy

Hereditary inclusion-body myopathy or distal myopathy with rimmed vacuoles (h-IBM/DMRV) is an autosomal recessive muscle disease caused by mutations in the UDP-N-acetylgalactosamine 2-epimerase/N-acetylmannosamine kinase (GNE) gene. Along with the typical phenotype, characterized by the involvement of distal leg muscles starting in early adulthood and quadriiceps sparing, uncommon presentations with non-canonical phenotype and unusual muscle biopsy findings are increasingly recognized. The aim of our study was to characterize pelvic and lower limb muscle involvement in h-IBM, thus providing clues for the diagnosis especially in the presence of atypical clinical or pathological features. We retrospectively evaluated muscle MRI or CT scans of a cohort of patients from different ethnicities, with distinct GNE mutations and different phenotypes. We found that severe involvement of tibialis anterior and biceps femoris short head is consistent even in early or atypical cases. Vastus lateralis, not the entire quadriiceps, was the only muscle spared in advanced stages, while rectus femoris, vastus intermedius and vastus showed variable signs of fatty replacement. Muscle involvement was generally symmetric. Some patients showed hyperintensities on T2-weighted sequences in T1-weighted completely or partially spared muscles. We described the pattern of muscle involvement in a group of h-IBM patients. Some characteristics were constant in all the subjects of our study. We believe their recognition may be useful in the differential diagnosis process with other myopathies and deserve validation in large prospective studies.

doi:10.1016/j.nmd.2011.06.886