year. No family consanguinity or history of neuromuscular diseases. Neurological examination revealed weak neck extensors (3/5) with dropped head syndrome, as well as, proximal weakness of the four limbs (4/5), atrophic quadriceps, tendon reflexes were 1+ and symmetric and plantar responses were flexor bilaterally. A myopathic gait was observed. Laboratory data showed serum CK level of 867 IU/liter, AST 56 IU/liter, ALT 52 IU/liter and Aldolase 11.6 IU/liter, ANA titer of 1:160. EMG showed a myopathic pattern. Deltoid biopsy revealed an inflammatory myopathy with a prominent B cell component. Treatment with prednisolone 1 mg/kg/day was associated with progressive improvement. We report a rare case of BCIM which improved with corticosteroid treatment. The pattern of inflammatory infiltrates observed in BCIM has several consistent features and can be missed because the disease is often patchy and altered by steroid use. Idiopathic inflammatory myopathies, as BCIM syndrome, are very important to consider in the differential diagnosis in all patients with muscle weakness because they are treatable.

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P5.34

Alternative splicing of lamin A leads to age-dependent accumulation of progerin transcript in normal human muscle and sporadic IBM

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Mutations in the lamin A gene (LMNA) cause limb girdle muscular dystrophies (EDMD2 and LGMD1B) and dilated cardiomyopathy as well as the Hutchinson-Gilford progeria syndrome (HGPS) of premature aging. In HGPS a de novo silent mutation at codon 608 activates an alternative splice site in exon 11 resulting in an internally truncated mRNA (A150 bases) and accumulation of a shorter lamin A isoform missing 50 amino acids, named progerin. Expression of progerin at low levels also occurs normally with aging in skin, liver and heart but has not previously been investigated in skeletal muscle. In this study we investigated whether there is age-dependent accumulation of progerin transcript in muscle biopsy samples from 13 healthy adults (37–71 years of age). RNA was extracted from biopsy samples and reverse transcriptase polymerase chain reaction (RT-PCR) was performed. Lamin A was consistently found in all samples. In addition, a product 150 bp smaller than lamin A, which was confirmed to be progerin by sequencing, was present in 7/13 samples. All individuals over 60 years of age had a progerin band with the youngest individual being 44 years. In view of the possibility that there is acceleration of the aging process in s-IBM muscle we also investigated biopsies from 7 s-IBM cases (aged 57–84 years) to determine if progerin expression is increased. Progerin amplicons were present in all 7 biopsies and the strongest progerin bands of the two groups were found in two of the s-IBM samples. These preliminary findings indicate that there is alternative splicing of lamin A and accumulation of progerin in skeletal muscle with aging and suggest that progerin expression may be increased in s-IBM.

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P5.35

Inclusion is accumulated by CHMP2B in sporadic inclusion body myositis

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Sporadic inclusion body myositis (sIBM) is a common inflammatory muscle disease in elderly person. Outstanding feature of sIBM is the presence of rimmed vacuoles (RV) revealed by modified Gomori trichrome staining and multiprotein aggregates made of amyloid β (Aβ) and ubiquitin in muscle fibers. RV are considered autophagic, since they often contain lysosomal membranous debris, an end product of muscle-fiber digestion, and increased immunoreactivity of some of the lysosomal enzymes. Autophagy is implicated in not only sIBM but also some frontotemporal dementia (FTD). In autophagy-lysosomal pathway, endosomal sorting complex required for transport (ESCRT) share a role in the transport of ubiquitinated protein to lysosome. Charged multivesicular protein 2B (CHMP2B), one of the subunits in ESCRT-pathway, was reported to be causative for FTD. We have reported that CHMP2B is a specific marker for granulocytocellular degeneration in Alzheimer disease (Yamazaki et al. Neurosci Lett 2010). In this study, we examined inclusions and RV among muscular disorders in terms of immunoreactivity for CHMP2B. The muscle biopsy specimens from sIBM (n = 5), distal myopathy with rimmed vacuoles (DMRV: n = 2), polymyositis (PM: n = 5), Duchenne/Becker muscular dystrophy (DMD/BMD: n = 5) were examined. In all cases, muscle samples had previously been examined by routine histochemical technique and immunohistochemistry. These specimens were subjected to immunohistochemistry and immunofluorescent technique, using antibodies against Aβ and CHMP2B. In sIBM and DMRV, inclusions and RV were immunopositive for CHMP2B. Double immunofluorescence staining showed a colocalization of Aβ and CHMP2B. A fraction of RV was stained by CHMP2B in PM. No structure was immunopositive for CHMP2B in DMD/BMD. This study suggests that the ESCRT-pathway is implicated in formation of aggregates in sIBM.

METABOLIC DISORDERS: POSTER PRESENTATIONS

P5.36

Standardized exercise test for identification of children with mitochondrial disorders

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Mitochondrial disorders result in impaired oxidative metabolism leading to lactate accumulation. Numerous studies have described physiologic responses to exercise, including blood lactate, in such patients. We devised a standardized protocol in order to differentiate children with mitochondrial myopathy who manifest abnormally high blood lactate concentrations at light and moderate levels of aerobic exercise from patients with non-mitochondrial myopathies and from healthy controls. The premise was that steady-state exercise done at power outputs of equivalent intensity across individual subjects would result in a blood lactate response which could then be related to measured oxygen uptake, the latter in turn reflecting tissue oxidative metabolism. We tested 6 patients with mitochondrial myopathy, 6 patients with non-mitochondrial myopathy, including 2 boys with Duchenne muscular dystrophy, 2 girls with minicore myopathy, 1 girl with limb-girdle muscular dystrophy and 1 girl with chronic fatigue of indeterminate etiology. Findings were compared with those observed in 28 healthy controls. Subjects performed an incremental cycle ergometer test to exhaustion on day 1. On a subsequent day they performed two, 6 min constant work-rate exercise bouts at one-third, then two-thirds, of...
Mitochondrial respiratory chain disorders (MRC), defined as primary diseases of the oxidative phosphorylation system are clinically, neuroradiologically, histologically, enzymatic and genetically heterogeneous. Then they are difficult to diagnose and classify. The aim of this study is to characterize the primary findings on histopathology of muscle biopsies performed in patients with definitive MRC. We include in this study the patients of our neurometabolic diseases consultation that fulfilled Walker’s criteria for definitive MRC and had performed a muscle biopsy. A total of 48 patients were assigned. The average age is 45.8 years and mean age at onset of symptoms was 25.4 years. 37.5% of the biopsies were considered normal. In the group of patients with clinically predominant muscle involvement (group 1), the biopsy showed changes consistent with mitochondrial disease in 82% of cases against 37.5% on the other patients (group 2). COX-negative fibers were found in 64% of patients of group 1 and 37.5% of group 2. In the first group, “red-ragged fibers” were seen in 71.4%, but only in sufficient number to be considered pathologic in 46.4%, while in the second group these numbers decreased to 50% and 25% respectively. Some other minor changes were seen, such as atrophy, blue-ragged fibers or an increase in the variability of fibers diameter. The group of 12 patients who still do not have a specific diagnosis is the one that shows fewer and more nonspecific changes in muscle biopsy. We emphasize that even in patients with normal biopsy, the molecular study of mtDNA in this tissue showed anomalies that supported the diagnosis. Muscle biopsy is an important study in all MRC disorders, and the study of mtDNA in this tissue showed anomalies that supported the diagnosis. Muscle biopsy is an important study in all MRC disorders, and there appears to be a good correlation between changes in it and a diagnosis of MRC with predominant involvement of muscle, thereby contributing to guide the study of these patients.

Mutations in the PEO1 gene, which encodes for the twinkle mitochondrial helicase, are a cause of autosomal dominant progressive external ophthalmoplegia (PEO) with accumulation of multiple mitochondrial DNA (mtDNA) deletions. To characterize the clinical features and molecular anomalies in a cohort of patients with twinkle mutations. Ten patients were analyzed, originating from 6 different families. In all of them a PEO1 mutation was searched by DNA sequencing, in peripheral blood (6 patients), or in muscle (1 patient), or in both of them (3 patients). A muscle biopsy was performed in 8 patients. In 6 of them a search for multiple deletions in mitochondrial DNA was performed using long range polymerase chain reaction (LR-PCR). The following analysis were performed: cardiological examination including electrocardiography (ECG) and echocardiography (9 patients), pulmonary function tests (6 patients), and electroneuromyography (7 patients). All patients were found to have PEO with ptosis and ophthalmoplegia. Six of them had bulbar symptoms with swallowing impairment. Permanent muscle weakness was found in 5 patients. Three of them complained of exercise intolerance. Mild axonal sensory neuropathy was detected in 4 patients. Only one of our patients had signs of mild hypertrophic cardiopathy and restrictive pulmonary dysfunction (VC = 74% of the predicted). Muscle biopsy showed ragged-red fibers or COX negative fibers in all patients. mtDNA multiple deletions were detected by LR-PCR in all cases but one. Genetic analysis of PEO1 gene revealed heterozygous missense mutations in exons 1, 2 and 3. The main clinical features observed in this cohort of patients with PEO1 mutations were PEO, swallowing impairment, mild limb muscle weakness and axonal sensory neuropathy. Cardio-respiratory, CNS and multisystem involvement seem to be rare.

Mutations in DNA polymerase-γ (POLG) can cause a wide range of diseases, showing a continuous spectrum of overlapping symptoms and signs, associated with mtDNA depletion and multiple deletions. Alterations in oxidative phosphorylation resulting from mitochondrial dysfunction have long been hypothesized to be involved in tumorigenesis. We report a 55-year-old man with adPEO and lung adenocarcinoma showing compound heterozygous POLG1 mutations. C. Pires, A.R. Silvestre, L. Vilarinho, L. Evangelista. "Hospital de Santa Maria, Neurology – Neuropathology, Lisbon, Portugal; "Hospital de Santa Maria, Neurology – Neurology, Lisbon, Portugal; Medical Genetics Institute, Oporto, Portugal

Mutations in DNA polymerase-γ (POLG) can cause a wide range of diseases, showing a continuous spectrum of overlapping symptoms and signs, associated with mtDNA depletion and multiple deletions. Alterations in oxidative phosphorylation resulting from mitochondrial dysfunction have long been hypothesized to be involved in tumorigenesis. We report a 55-year-old man with adPEO and lung adenocarcinoma showing compound heterozygous mutations (T251I-P587L/P648R) in POLG1 gene. A 55-year-old male presented with progressive bilateral ptosis and dysphagia. Four years later he also noted muscle weakness and fluctuant dysphonia. His father and paternal grandfather also had bilateral ptosis and presumably died due to cancer. Neurological examination revealed bilateral ptosis, external ophthalmoplegia, pigmentary retinopathy and moderate weakness of the neck, distal upper limbs and proximal lower limbs. Muscle histology disclosed ragged red fibres and COX-deficient fibres. Southern blot analysis showed multiple mtDNA deletions in muscle. Sequence analysis of POLG1 gene revealed three compound heterozygous mutations T251I-P587L/P648R, all previously recognized as pathogenic. Five years later a lung adenocarcinoma was diagnosed and a resection surgery was performed with good clinical outcome. Although the T251I-P587L mutation in cis is frequently described as a recessive allele, an autosomal dominant mode of inheritance has also been reported. In this family, we assume the latter hypothesis as a dominant transmission is suspected. The association of P648R, previously reported in arPEO, with T251I-P587L may have led to a more severe phenotype. In a previous work, POLG gene was mutated in 63% of breast tumors and mutations were found in all

P5.37 Characterization of muscle biopsies in Mitochondrial respiratory chain disorders
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P5.38 Clinical features of autosomal dominant ophthalmpoplegia related to PEO1 gene mutations
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P5.39 Autosomal dominant chronic progressive ophthalmoplegia (adPEO) and lung adenocarcinoma showing compound heterozygous POLG1 mutations
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