to diastase digestion. Electron microscopy revealed very high subsarcolemmal and intermyofibrillar accumulation of glycogen. There was no lactate increase during the grip test, and grip strength was reduced to less than one third of normal strength. An in vitro glycogenolysis/glycolysis study was performed on muscle and revealed a metabolic block below fructose 6 phosphate. PKF activity in muscle was totally absent. A new homozygous mutation was detected in PFKM gene (c.165T > A) inducing a premature stop codon (p.Tyr55X) probably responsible for a precocious mRNA degradation (mRNA decay phenomenon). Early-onset fixed muscle weakness may be a predominant clinical feature of PKF deficiency. Vascular myopathy with polysaccharide deposits remains an important morphological hallmark of this rare muscle glycogenosis.

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P5.49
Adult onset intermittent rhabdomyolysis
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Deficiency of very-long-chain acyl-CoA dehydrogenase (VLCAD), which catalyzes the first step of mitochondrial fatty acid oxidation, is inherited as an autosomal recessive trait. The most common phenotypes occur in neonatal period or childhood, presenting with cardiomyopathy, hepatomegaly and hypoketogenic hypoglycemia. The juvenile/adult-onset is characterized by exercise intolerance and recurrent rhabdomyolysis triggered by prolonged exercise or fasting. Since VLCAD deficiency was included in neonatal screening, seven cases were diagnosed in Portugal, between 2004 and 31th August 2010 (incidence of 1:73.244 per 512.705 newborns). 51-year-old caucasian male, without consanguinity or relevant family history, presented in adolescence, with recurrent myalgia, weakness and muscle contractures triggered by intense physical exercise and prolonged fasting. Since the age of 20, he had four episodes of severe rhabdomyolysis, the last one complicated with acute renal failure requiring dialysis. The neurological evaluation was normal between the episodes. Laboratory evaluation showed normal plasma creatine kinase and normal renal function in asymptomatic periods and increased plasma pyruvate/lactate ratio with an increase in the pyruvate after ischemia. Electromyography and muscle biopsy were unremarkable. The acylcarnitines profile was consistent with a deficiency of VLCAD, confirmed by genetic test. Mitochondrial beta-oxidation defects result in metabolic myopathies and pose a diagnostic challenge due to their transient clinical and laboratory manifestations and the absence of morphological changes in muscle biopsy. This is the first case of late-onset myopathic phenotype diagnosed in Portugal, there are only seven other cases of VLCAD in Portugal all diagnosed with neonatal screening program. We highlighted the adult phenotype of VLCAD deficiency, emphasizing the need of a high index of suspicion.

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MYOFIBRILLAR MYOPATHIES: POSTER PRESENTATIONS

P5.50
Clinical Lipidomics – An approach towards clinical readout in orphan an common neuromuscular diseases
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A clinical and biochemical review of patients for systematic metabolic and molecular analyses with orphan neuromuscular diseases including lipid-storage-myopathies. Four subtypes of hereditary Lipid-Storage-Myopathies (LSM) are currently known. The clinical symptoms range from minimal muscular weakness to muscular pain and severe systemic deficits, often combined with very high plasma levels of creatinkinase. Validation of subtypes is essential, as therapy is achievable. In, e.g. primary carnitine-deficiency (PCD), clinical symptoms and disease progress can be improved by substitution of carnitine. In primary or secondary coenzyme Q10-deficiency coenzyme Q-10 and riboflavin can be substituted and also improves muscular weakness, muscular pain and possibly progress of disease. To evaluate clinical profiles combined with metabolomics discernable patterns should be detected that correlate with diagnosis and perhaps progression of LSM. In the first step 10.754 reports of muscle biopsies from past 25 years were data mined to detect patients with LSMs. In total 49 patients were detected, 16 were able to participate in this study. In the second period blood samples from 252 neuromuscular patients including verified LSD were collected, following a trial to compare the data of these patients by clinical manifestations (phenotypes) and metabolomics with patients with and without other neuromuscular diseases. The blood samples of non-myopathy-patients serve as reference samples to create models for the mitochondrial involvement. Phenotypes of groups compares myopathies with the subgroup LSM, and neuropa-thies. Patients with LSM predominantly show a distinct pattern of proximal upper extremity muscle weakness, whereas other myopathies are often characterized by more generalized weakness and atrophy. Further steps of comparison of the lipid-metabolism at different levels (RCC 1–V, Co-Q10, CoA – β-oxidation) will follow.

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Reducing bodies and myofibrillar myopathy features in FHL1 muscular dystrophy

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Mutations in the FHL1 have been associated with diverse chronic myopathies including late onset X-linked and scapuloperoneal muscular dystrophy with bent spine syndrome, reducing body myopathy, X-linked dominant scapuloperoneal muscular dystrophy, rigid spine syndrome, and contractures and cardiomyopathy mimicking Emery-Dreifuss muscular dystrophy. Myofibrillar myopathies (MFMs) are morphologically distinct but genetically heterogeneous muscular dystrophies arising from mutations in Z-disc related proteins. Because some pathologic features of the FHL1 dystrophies and the MFMs overlap, we searched for mutations in FHL1 in our cohort of 50 genetically undiagnosed MFM patients. We detected two novel and one previously identified missense mutation in our cohort of 50 genetically undiagnosed MFM patients. All but one patient presented with progressive muscle weakness: one had hypertrophied muscles, rigid spine, and joint contractures, and one also had a peripheral neuropathy. Patients harboring LIM2 domain mutations also display menadione-NBT positive reducing bodies whereas the patient whose mutation falls outside the LIM domain also shows disordered Z-disc proteins. Desmin staining showed large intracellular aggregates. This family is expanding the phenotype and morphotype of the X-linked myopathy with postural muscle atrophy (XMPMA) caused by the C224W mutation in the FHL1 gene. We would like to suggest to term all FHL1 gene associated myofibrillar myopathies as FHL1opathies.

Myofibrillary myopathy (MFM) is a group of heterogeneous muscle disorders pathologically characterized by disorganized myofilaments and protein aggregations. Several genes encoding Z-disc proteins were identified in patients with MFM including BAG3. So far, only a heterozygous p.Pro209Leu mutation has been the only BAG3 mutation identified. Patients with this mutation show early onset progressive limb and axial muscle weakness, cardiomyopathy and severe respiratory insufficiency. We report herein two unrelated patients with different novel BAG3 mutations. Patient 1 is a 7-month-old boy with a heterozygous p.Ala558Val mutation showed reduced fetal movement and was born at 38 weeks of gestation with severe asphyxia. He manifested hypotonia, joint contractures and severe respiratory insufficiency which required artificial ventilation. Serum CK levels shifted 200 to 3000 U/L and transient ventilatory enlargement were seen. Muscle biopsy showed many cytoplasmic bodies and disorganization of myofilaments. Patient 2 is a 67-year-old woman with a heterozygous p.261–265RAASP deletion. From 60 years of age, photophobia, diplopia, ptosis, ophthalmoplegia and weakness of orbicularis oculi and lower limb muscles gradually appeared. Myasthenia gravis were excluded by electrophysiological study and anti-AChR antibody evaluation. Serum CK level was 84 U/L and EMG showed myogenic changes. Muscle biopsy showed many intracellular aggregations and disorganization of myofilaments. This is the first adult-onset MFM with deletion mutation in BAG3.

Myotilin, a muscle-specific Z-disc protein, has roles in myofilibr assembly and stabilization of sarcomere. Mutations in the myotilin gene (MYOT) have been associated with limb girdle muscular dystrophy type 1A, myofibrillar myopathy (MFM), and distal myopathy. Myofibrillar disorganization and accumulation of Z-disc proteins are characteristically