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Natural history of McArdle disease: a single centre study of a cohort of 220 patients

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McArdle disease is caused by recessive mutations in *PYGM* gene. The condition is considered to cause a 'pure' muscle phenotype with symptoms including exercise intolerance, inability to perform isometric activities, contracture, acute rhabdomyolysis. However, studies aiming to describe extra-muscular manifestations are rare. In this study we extensively describe phenotypic and genotypic features of a large cohort of people with McArdle disease, all attending the Highly Specialized McArdle Disease and Related Disorders service at the National Hospital for Neurology and Neurosurgery, London. We retrospectively assessed case records of 220 patients with a confirmed diagnosis of McArdle disease between 2011-2019 and report data relating to genotype and phenotype, including frequency of rhabdomyolysis, fixed muscle weakness, gout and unexpected comorbidities inclusive of retinal and thyroid disease.

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Automated image-analysis method showed positive correlation between body mass index and skeletal muscle fiber size in humans

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The quantitative analysis of muscle histomorphometry has been growing in importance in both research and clinical settings. Accurate and stringent assessment of myofibers' changes in size and number, and alterations in the proportion of oxidative (type I) and glycolytic (type II) fibers is essential for the appropriate study of aging and pathological muscle, as well as for diagnosis and follow-up of muscle diseases. To explore mechanisms leading to obesity sarcopenia, we investigated the variations of muscle fiber size according to body mass index (BMI). For this aim, we included 75 consecutive patients with histologically normal deltoid muscle at biopsy. Four-channels immunofluorescence technique was carried out on cryosections using antibodies directed towards myosin heavy chain (MHC)-type I, MHC-IIa, MHC-IIx, and dystrophin. Macro script for Fiji-ImageJ, allowing automatic assessment of human fiber morphometry in digital images of the entire muscle biopsy samples, was applied to quantify muscle fiber size according to subtypes. Sex-ratio was 34M/41F. Age ranged from 18 to 83 (age<22: n=2; age 20-39: n=24; age 40-59: 29; age≥60: n=20). BMI ranged between 17.4 to 42.5 (<25: n=40; 25-29.9: n=18; n>30: n=17). Myofiber size (cross section area [CSA], minor diameter [minD]) was higher in males compares to females (Type I: $p<0.05$; IIa and IIx: $p<0.0001$). We found a positive correlation between BMI and myofiber size (CSA, minD), the strongest correlation being observed for type-IIx fibers (CSA: $p=0.0007$; minD: $p=0.0004$). In conclusion, our four-channels macro appeared fully suitable for the study of human skeletal muscle to analyze the effects of obesity on skeletal muscle.

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A rare cause of exercise-induced rhabdomyolysis: very long chain acyl-CoA dehydrogenase deficiency

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Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) is a rare disorder of fatty acid metabolism characterized by hypoglycemia, liver failure, cardiomyopathy, and rhabdomyolysis. Herein, we report a case who had presented with exacerbation-induced rhabdomyolysis attacks since childhood and diagnosed with VLCADD. A 17-year-old boy presented with getting tired quickly, myalgia in lower limbs and dark brown urination following prolonged exercise. He was born after uneventful pregnancy and delivery, with consanguineous marriage of his parents. There was no family history of neuromuscular disease. Between acute episodes, the patient was asymptomatic with normal neurologic examination and laboratory findings. In the last episode, serum creatine kinase level was 54676 U/L and decreased after intravenous fluids and rest. The other biochemical tests, echocardiography and tandem mass spectrometry, were unremarkable. We identified a homozygous mutation of c.883_835delAGA (p.Lys278del) in exon 9 of the *ACADVL* gene. With all these clinical and laboratory findings, he was diagnosed with VLCADD. Exercise-induced rhabdomyolysis may be fatal. Therefore, it is necessary to investigate the underlying causes. The rare causes of rhabdomyolysis such as long-chain fatty acid oxidation disorders, glycogen storage diseases (Type V-McArdle disease), carnitine metabolism disorders (Carnitine palmitoyltransferase II deficiency), lipin-1 deficiency, mitochondrial disease, myoadenylate deaminase deficiency should also be considered. Tandem mass spectrometry test may be helpful in fatty acid oxidation defects in an acute attack of rhabdomyolysis. But a next generation sequencing test may be necessary to detect long chain fatty acid oxidation defects in suspected cases.

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MITOCHONDRIAL DISEASES

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The analysis of mitochondrial respiration and membrane potential in skeletal muscles of Huntington disease patients

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The development of Huntington's disease (HD) is associated with muscle pathology, manifesting in wasting and atrophy, and accompanied by defects in energy metabolism. However, the precise mitochondrial respiratory chain alterations have not been yet defined for different stages of HD development in patients. Muscle samples were acquired by a fine-needle biopsy method from the middle part of the m. rectus femoris of 8 HD pre-symptomatic patients (age, mean±SD, 27±3.25 years), 8 symptomatic patients (43.1±5.59 years) and 15 age and sex-matched controls (28.5±3.21 years, matched to pre-symptomatic; 40.3±5.59 years, matched to symptomatic) for further analysis. Following mechanical preparation and permeabilization with saponin, changes in mitochondrial membrane potential (mtMP) were assessed simultaneously with respiration measurement using cell-permeant, cationic dye TMRM (tetramethylrhodamine, methyl ester), and high-resolution respirometry system Oroboros Oxygraph-2k (Oroboros Instruments, Austria). The data were normalized to the wet weight of samples; results (pmol O2/s/mg, means±SD) were statistically analyzed using the Mann-Whitney test. The coupled respiration rates (both CI- and CI+CII-related respiration during oxidative phosphorylation) were lower in pre-symptomatic patients when compared to matched controls and symptomatic patients (CI: 20.7±2.7 vs. 26.6±2.0 and 27.9±6.5, $p<0.001$ and $p=0.001$; CI+CII: 34.3±4.4 vs. 44.8±7.5 and 46.1±5.6, $p=0.007$ and $p=0.001$). However, the dynamics of mtMP were on the same level in pre-symptomatic and symptomatic patients, and only the tendency to less pronounced changes in mtMP was observed in pre-symptomatic and symptomatic patients in comparison to matched controls. The study showed that alterations in