(childhood) dermatomyositis (DM), non-specific or overlap myositis (NSM), and necrotizing autoimmune myopathy, which can also develop in childhood. Muscle weakness develops within weeks to months in a symmetrical and proximal distribution in arms and legs, starting in the hip flexors and/or shoulder abductors, and extending to the neck flexors and distal muscles. In (childhood) DM, the presence of periorbital heliotrope edema and a rash over the extensor surfaces of the hands, fingers, elbows and knees (Gottron papules or Gottron sign) is sufficient for the diagnosis. In patients without characteristic DM skin rash or with a myositis in association with a known connective tissue disease, a muscle biopsy is necessary to confirm the diagnosis. We present three childhood-onset cases in whom there was considerable diagnostic delay. Patients presented with a long-standing limb-girdle distribution of moderate to severe muscle weakness including scapular alae which initially hindered a correct diagnosis. A diagnosis of a muscular dystrophy, Pompe’s disease or congenital myopathy was considered. Subsequently, a muscle biopsy was found to be consistent with a late stage dermatomyositis in two patients and non-specific myositis in the third. All three patients made a good recovery after treatment with immunosuppressive and immunomodulating therapy. These cases illustrate that IIM can have a protracted course with an atypical presentation. It is of importance to recognize these clinical syndromes as IIM are treatable disorders.

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G.P.208
Early onset autoimmune necrotizing myopathy associated with anti-HMGCR antibodies: An unmissable diagnosis


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Antibodies against HMGCR, the pharmacological target of statins, were identified by Mammen et al. in a cohort of adult patients suffering from immune-mediated necrotizing myopathy (IMNM). Most of these patients were exposed to statins. More recently, HMGCR antibodies have been identified in a series of European patients with IMNM, including statin-naïve patients among whom there were some children and young patients initially considered as suffering from a limb girdle muscular dystrophy. We aimed to describe a series of young patients suffering from IMNM associated with HMGCR antibodies mimicking a limb girdle muscular dystrophy. Four female patients presented with slowly progressing proximal muscle weakness in four limbs. Age at onset varied from 5 to 28 years; age at the time of diagnosis varied from 11 to 31 years; and diagnosis delay varied from 1.5 to 25 years. Serum CK levels at the disease onset were highly elevated (8000–12 000 IU/L) in all patients. Muscle biopsies revealed muscle fiber necrosis and regeneration, increased endomysial connective tissue, and sparse or no inflammation. MHC class I was up-regulated in two patients. None of our patients had extramuscular symptoms, and none had any known myositis-specific or myositis-associated antibodies. Three patients had a very long-lasting disease, up to 25 years, and were considered as suffering from a limb girdle muscular dystrophy. However, no protein or gene defect could be identified. Testing the four patients for HMGCR antibodies revealed positive titers, thereby allowing us to establish the correct diagnosis and initiate immunomodulatory treatment. Early onset IMNM associated with HMGCR antibodies must be included in the differential diagnosis in children and young patients suffering from limb girdle weakness with no molecular diagnosis, as its recognition may result in starting potentially effective treatment.

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G.P.209
Plasma IP-10 level distinguishes inflammatory myopathy

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Discrimination of idiopathic inflammatory myopathy (IIM) from other muscle diseases is at times difficult in clinical practice even after muscle biopsy. Here we aim to identify a biomarker to distinguish IIM from other muscle diseases. We studied 100 IIM patients, including polymyositis (n = 19), dermatomyositis (n = 19), anti-synthetase syndrome (n = 8), immune-mediated necrotizing myopathy (n = 17), and inclusion body myositis (n = 37). As non-IIM controls, we enrolled 50 patients with hereditary muscle diseases (hMD), including Duchenne/Becker muscular dystrophies (n = 6), limb-girdle muscular dystrophies (n = 7), facioscapulohumeral muscular dystrophy (n = 25), congenital muscular dystrophy (n = 1), and GNE myopathy (n = 12). We measured 27 cytokines in the plasma of the patients by using a Bio-Plex technology. We found that plasma levels of IP-10 and etoxacin were significantly higher in every IIM than hMD (p < 0.01). There were no significant differences among subtypes of IIM or significant correlation between the cytokine levels and patients’ age. Receiver operating characteristic analysis revealed that IP-10 had a larger area under the curve on IIM than etoxacin: 0.96 (95% CI: 0.92–0.99, p < 0.0001) versus 0.88 (95% CI: 0.81–0.94, p < 0.0001). When the cut-off level of IP-10 was set at 650 pg/ml, showing the best accuracy, the sensitivity and specificity were 91% and 90%, respectively. This study demonstrates that plasma IP-10 level can distinguish IIM from hMD with high sensitivity and specificity.

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G.P.210
Myopathy with anti-signal recognition particle antibodies: Clinical and HLA associations in Malaysian patients

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Anti-signal recognition particle (SRP) antibody associated myopathy is a complement dependent antibody-mediated necrotizing myopathy which is often clinically more severe and requires longer and more aggressive immunosuppressive treatment. We describe the clinical, serological and HLA gene associations of anti-SRP associated myopathy seen in the multiethnic Malaysian population. Consecutive patients with biopsy-proven myositis were tested for anti-SRP and other myositis specific antibodies (MSA). Low-resolution single-specific primer-polymerase chain reaction (SSP-PCR) was carried out to type for class II HLA alleles in anti-SRP myopathy patients and normal healthy controls. Odds ratios (OR), 95% confidence intervals (95% CI), and P values to test for significance were computed using SPSS software. Of the 45 patients with inflammatory myopathy seen between 2012 and 2014, 12 (26.7%) were positive for anti-SRP antibodies. Ten (83.3%) were female; seven (58.3%) were ethnic Chinese, four (33.3%) ethnic Malay and one (8.3%) ethnic Kadazandusun. Mean age of onset was 35.8 (range 16–60 years) and mean creatine kinase was 6785 u/L (range 385–7080). Other associated MSA were found in nine (75%) patients and included anti-PL7, PL-12, Ku, PMScl-75, PMScI-100 and Ro52. Extra skeletal muscle involvement included skin rash (two patients), respiratory symptoms (two patients) and Sjogren syndrome and SLE (one patient each). None had associated cardiac disease or malignancy. HLA genotyping results showed an association with HLA-DRB1*08 allele (P = 0.048, OR = 4.31, 95% CI = 1.19–15.58) in Chinese patients, and with HLA-DRB1*12 allele (P = 0.0393, OR = 4.46, 95% CI = 1.06–18.68) in Malay patients. Anti-SRP associated myopathy appears to be frequent, seen in native and ethnic Chinese
G.P.211
Effects of auto-antibodies anti-signal recognition particle (SRP) and anti-hydroxymethylglutaryl-CoA reductase (HMGCR) on muscle cells

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Necrotizing myopathies (NM) might be acquired auto-immune muscle diseases, in which muscle biopsy demonstrates marked muscle necrosis with regeneration, little or absence of inflammatory infiltrates and a particular pattern of complement C5b-9 deposition on muscle fibers. NM can be seropositive for some auto-antibodies (aAbs) such as anti-SRP as well as anti-HMGCR. The titer of those Abs is correlated with the creatine kinase levels, but their role remains unclear. In the current study, we investigated the effect of the aAbs anti-SRP and anti-HMGCR on in vitro primary human myoblasts/myotubes. Primary human myoblasts were isolated from human muscle biopsies of nonmyopathic patients. Myoblasts were sorted by CD56 immune-magnetic microbead Abs. To study the effect of the auto-Abs on muscle cells, confluent myoblasts and 3 day myotubes were incubated with anti-SRP or anti-HMGCR positive human IgG for 72 hours or with IVIg as a control. We demonstrate that the addition of the aAbs onto differentiated myotubes leads to atrophy, as measured by the reduction of the size of myotubes (anti-SRP 66.5 ± 2.6 μm², anti-HMGCR 66.5 ± 4.8 μm² vs control 118.8 ± 6.1 μm², p < 0.001). The expression of atrophic genes as Atrogin and Murf-1 was measured by qPCR; the culture with anti-SRP Abs shows an increase of Atrogin expression and the anti-HMGCR shows an increase of Murf-1 compared to the control. Furthermore, addition of the aAbs to a confluent myoblasts significantly reduced the capacity of myoblasts to differentiate (anti-SRP 44.2 ± 7.7 μm², anti-HMGCR 53.6 ± 7.7 μm² vs control 147.8 ± 5.4 μm², p < 0.001). These findings suggest that anti-SRP and anti-HMGCR aAbs have a pathogenic effect on muscle cells in vitro by both inhibiting cell fusion and triggering atrophy on fully differentiated myotubes.

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G.P.214
Fasciitis frequently accompanies myopathy in acute critical illness muscle wasting: Evidence from qualitative ultrasound and muscle biopsy analysis

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A rapid and early loss of skeletal muscle mass underlies the physical disability that is common amongst survivors of critical illness (CI). The functional capacity of skeletal muscle depends on its quantity as well as quality, which may be adversely affected. Our main objectives were to characterise changes in muscle echogenicity, pennation angle and fascial characteristics that occur early in CI, and to relate these to histologically defined myofibre necrosis and fascial pathology. Subjects comprised a subgroup of patients recruited to the Musculoskeletal Ultrasound in CI: Longitudinal Evaluation (MUSCLE) study. Comparisons were made between sequential Vastus Lateralis (VL) biopsy specimens and ultrasound assessment of Rectus Femoris (RF) echogenicity. Change in RF pennation angle was measured. In 30 patients, change in muscle echogenicity was greater in patients who developed muscle necrosis than in those who did not [8.2% (95% CI 5.3 to 21.7) versus −15.0% (95% CI −28.9 to −1.09), p = 0.016]. The AUROC for prediction of myofibre necrosis was 0.74 (95% CI 0.565–0.919, p = 0.024) increasing to 0.85 (95% CI 0.703–0.995, p = 0.003) with the removal of those with potential iatrogenic muscle damage. Fasciitis was observed in 18 out of 30 biopsies (60%) and was dominated by macrophages by day 7 or day 10. Mean pennation angle decreased from 7.6° ± 4.0 to 5.5° ± 2.1 (p = 0.01) over the first 10 days of CI. Myofibre necrosis and fascial inflammation can be detected noninvasively using ultrasound in CI. Fasciitis precedes and frequently accompanies muscle necrosis and is dominated by macrophages in the late acute phase. Rapid decreases in pennation angle are seen. These findings may have functional implications for survivors of critical illness.

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DMD BIOMARKERS

G.P.213
Glutathione imbalance in blood of patients with Duchenne muscular dystrophy

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Oxidative stress may contribute to muscle degeneration in Duchenne muscular dystrophy (DMD) and may influence the disease progression and severity. In the past few years antioxidant drugs have been proposed as potential therapeutic strategy for DMD and several clinical trials with different compounds are ongoing. Glutathione is the main nonprotein antioxidant in cells, mostly occurring in its reduced form (GSH) that can be oxidized to GSSG under oxidative stress. The GSH/GSSG ratio is critical and must be balanced, with GSH exceeding 100/1 the GSSG. Glutathione is a highly sensitive redox indicator and represents a non-invasive and reliable systemic biomarker also in monitoring clinical trials. The objective of the study is to assess the plasma levels of total, reduced, and protein-bound glutathione and the glutathione-related antioxidant enzyme activities, plasma thiols and carbonyl content in DMD patients. The results are that we analyzed GSH and GSSG levels in whole blood of 12 DMD patients. Blood GSH concentration was consistently decreased in DMD patients with respect to the controls (p < 0.001), whereas its oxidized form (GSSG) was significantly increased (p < 0.0001). Accordingly, plasma thiols and glutathione peroxidase enzyme, which requires GSH as a co-substrate for its detoxifying activity, were further decreased in patients. These results strongly support the involvement of the oxidative stress in the downstream cascade to dystrophic pathology and indicate glutathione as an efficient systemic redox biomarker. Blood GSH and GSSG should be considered and validated as surrogate non-invasive biomarkers to test the efficacy of antioxidant treatments.

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G.P.214
Brain metabolite concentrations in Duchenne muscular dystrophy are unaltered compared to controls

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Duchenne muscular dystrophy (DMD) is associated with specific learning and behavioural disabilities. We have previously reported reduced grey matter volume, altered white matter microstructure and reduced cerebral blood flow in DMD patients compared to healthy age-matched controls. In these findings, the