P06- 93- Case report of ?double trouble? patient- combination of Ullrich congenital muscular dystrophy and spastic ataxia Charlevoix-Saguenay type.

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We present a case report of a five year old boy of a Russian origin with symptoms of Ullrich CMD. He was born with floppy infant signs and had motor delay at first year of life. Our patient started to walk independently since 23 months, had gait disturbances and muscular wasting and could not get up if fallen. He also had drop head syndrome and have been able to control his head only at 3-3,5 y.o. He developed funnel chest deformity, ankles, knees, hips, shoulders and elbows contractures in combination with hyper elasticity in phalangeal joints. Skin abnormalities included follicular hyperkeratosis on the hips, ankles, shoulders, arms, and face; a rough keloid scar appeared after muscle biopsy on the right hip. Muscle tone was diffusely reduced, DTR were not presented. CK level was within a normal range (164, 176 U/l). Muscle MRI showed diffuse fat replacement in hips and ankles with a ?tiger? pattern, very specific to collagen VI. The only test not confirming Ullrich CMD was EMG study. EMG registered MUAP's with median amplitude 2696 mV, and maximum amplitude 4683 mV, and signs of progressive loss of motor units. It was unexpected as we did not expect neurogenic disorder in our patient. All types of SMA related to SMN gene were excluded. NGS was performed and we found 3 mutations in COL6A2 gene (mutations related to Ullrich CMD) and 3 mutations in SACS gene (mutations related to spastic ataxia Charlevoix-Saguenay type). All motor development features, clinical features, CK level and MRI findings could be explained by collagenopathy- mutations in COL6A2 gene, but not EMG results. Neurogenic changes in our patient's EMG may be explained by SACS mutations that could be a cause of the specific pathway of this slow current neurogenic disorder. Vermis atrophy and degeneration of cerebellar hemispheres leads to pyramidal tract suffering and subsequent degeneration of the lower motor neuron, which damage we observed on the needle EMG. Usually patients with spastic ataxia Charlevoix-Saguenay type are characterized with cerebellar ataxia, nystagmus, lesions of pyramidal tracts, spasticity, high DTR and peripheral neuropathy. Cognitive functions are not involved. Sometimes it can be an atypically late onset or peripheral neuropathy only. We think that our patient has both disorders, with clinical features of Ullrich CMD dominating at present, co-existing with spastic ataxia Charlevoix-Saguenay type, which may become more active later and complicate Ullrich CMD.

Ullrich congenital muscular dystrophy, spastic ataxia Charlevoix-Saguenay type, COL6A2 gene, SACS gene, neurogenic changes, EMG, MUAP's, muscle MRI,

P07- Distal myopathies / Myofibrillar myopathies- N° 94 to N° 103

Distal myopathies- #4466

P07- 94- Decline in Upper and Lower Extremity Muscle Strength Observed Over 1 Year in a Prospective, Observational GNE-Myopathy Natural History Study

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GNE Myopathy (GNEM) is a rare, severely debilitating adult-onset myopathy with progressive muscle weakness caused by a mutation in the GNE gene that encodes an enzyme critical to the biosynthesis of sialic acid (SA). To gain a better understanding of the clinical presentation and progression of the disease, a natural history study was initiated in 2014. Up to 100 subjects are planned to be enrolled and followed for a minimum of 3 y under a research protocol.

This is an international, prospective, observational study in subjects with genetically confirmed GNEM. Five study sites in North America and Europe are participating. Enrolled subjects may continue to take substances they feel provide benefit and may participate in clinical trials of investigational products for GNEM treatment. Muscle strength was measured by hand held dynamometry (HHD) at baseline, 6, and 12 months during the first year and then yearly thereafter. Individual muscle group strength in the upper extremities (grip, shoulder abductors, elbow flexors and extensors) and lower extremities (hip flexors, extensors, abductors, adductors, and knee flexors) were combined to generate composite scores (UEC and LEC). Strength was compared with age- and gender-matched normative values.

A total of 48 subjects who had completed 12 months of follow up were evaluated. The mean age of subjects was 41 y, 56% were men, and most were white (94%). Eighteen subjects (37.5%) could walk ?200m in the 6-minute walk test (6MWT) at baseline; 30 subjects (62.5%) could walk

In this broad cohort of subjects with GNEM, substantial muscle strength impairment was observed at baseline and declined measurably over 1 y in both the upper and lower extremities, regardless of walking ability. These findings are consistent with other observational studies of GNEM showing the progressive decline of muscle strength in a period as little as 1 y.

GNEM, hand held dynamometry, sialic acid, natural history study

Distal myopathies- #2408

P07- 95- MicroRNA regulation of the GNE gene

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MicroRNAs (miRNAs) have a definite role in muscle biology, as fine tuning regulators of functions involving homeostasis in muscle tissue. To date, there is no data related to a possible role of miRNAs in GNE regulation or in GNE Myopathy pathophysiology. GNE is expressed ubiquitously and could be the target of diverse miRNAs. If GNE is targeted by myomiRs (muscle specific miRNAs) this could mean that GNE, in addition to its enzymatic role in the biosynthesis of sialic acid in all tissues, has a specific role in muscle.

To explore this hypothesis we have first analyzed in silico the 3'UTR of human GNE for potential miRNAs binding sites. After identifying 2 conserved sites for miRNA-1 and miRNA-96 respectively, we have validated their specific sequence target in GNE by the luciferase functional assay. MiRNA-1 is well known for its particular role in muscle tissue, thus the fact that it can regulate GNE expression strongly supports a role for GNE specifically in muscle. Further, both miRNAs known target genes include several genes involved in biological pathways important in muscle, therefore it could be that also GNE is involved in these biological pathways. Screening for expression of these 2 miRNAs in muscle cells from GNE Myopathy patients showed no statistically significant differences compared to the same cells from control individuals, thus the role of these miRNAs in the pathophysiology of the disease is not clear yet.

To broaden our knowledge on the role of miRNAs in GNE Myopathy, we have performed RNA sequencing on these same GNE Myopathy patients muscle cells. Bioinformatic analyses has pointed to differentially expressed miRNAs compared to control muscle cells, and their targets are now being analyzed.

Deciphering the GNE mechanisms underlying muscle function is an important challenge. We anticipate that at least some of the genes/pathways/functions unravelled in these studies will give better insights on the possible pathophysiological mechanisms of GNE Myopathy and that at least some of them could eventually be addressed as treatment targets.

microRNAs, GNE, GNE Myopathy, mir1, mir96

Distal myopathies- #2497

P07- 96- Myoshi myopathy: a rare mutation in a brazilian patient- case report

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Myoshi myopathy is a heterogenous group of recessive dystrophies caracterized by the absence of a protein linked to muscle membrane called dysferline.
The clinical picture includes distal weakness beginning in early adulthood affecting mainly gastrocnemius and soleum muscles, difficulting in standing on tip toes. The disease progression leads to proximal weakness sparing hand muscles.
The diagnosis is obtained by clinical features, muscle biopsy associated with loss of dysferline expression evidenced by Western-blotting and/or immunohistochemistry.
The presence of a mutation on cromossome 2p13 confirmes the diagnosis.
Objective: Describe a rare mutation in a brazilian patient.
Case report:
We report a 28-years-old Caucasian woman with slowly progressive muscle weakness and wasting of his posterior calf muscles since she was 12 year old. At age 23 year old she had difficulty in standing on tip toes and at age 28 she was not able walking on tip toes. Neurological examination revealed weakness 3 out of 5 in his posterior calf muscles and proximal weakness 5- out of 5 in his anterior calf muscles. In the upper limbs we noted a scapula alata and proximal weakness 5- out of 5. His deep tendon reflexes were preserved. His family history was suggestive for an autosomal recessive trait.
Serum creatine kinase level was elevated. Muscle biopsy of anterior tibial muscle revealed myopathic changes including marked variation in fiber size, internally localized nuclei, and necrotic and regenerating fibers. Dysferlin immunoreactivity was absent at muscle fiber membranes. The magnetic resonance imaging revealed atrophy and fatty replacement mainly of the gastrocnemius and soleus muscles.
Conduction studies were normal and needle EMG was myopathic.
DNA extraction and direct sequencing of the complete dysferlin gene was done and a deleterious pathogenic mutation was localized in exon 52 of DYSF gene in heterozigosis. It was a frameshift mutation defined as c.5813_5821delCAGCCAAGA. We also founded a missense mutation in exon 12 of DYSF gene defined as c.1168G>A.
Discussion: DYSF is a large size gene and presents more than 300 different sequence variants, including deleterious mutations and known pathogenic polymorphism. Althought 66% of patients have two common mutations, our patient showed two rare mutations. Therefore methods for mutations screening are particularly useful for eficient molecular analysis on a routine basis.

Myoshi, myopathy, dysferline

Distal myopathies- #2587

P07- 97- Severe axial muscular involvement in Laing myopathy

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Mutations in the MYH7 gene are implicated in a heterogeneous group of diseases, which include Laing Distal Myopathy (LDM) that is characterized by more prominent weakness in the tibialis anterior, long toe extensor, neck flexor and finger extensor muscles. Axial muscle involvement can also be found as a late presentation. Here we describe four patients from three Brazilian families with mutations in exon 34 of the MYH7 gene, including one mosaic. The heterozygous mutation c.4802T>C (p.Leu1601Pro) was found in patient 1, and the c.4814G>GC (p.Arg1608Pro) in patient 2; patient 3 is father of patient 2 and had the same mutation but in a mosaic pattern. The mutations c.4822C>A (p.Arg1608Ser) and c.4833C>A (p Ala1611Asp) were found in patient 4. Patients 1 and 2 share similar clinical features and muscle imaging findings. Both have a predominant distal muscle weakness and a very severe and early axial involvement. Muscle MRI showed symmetric and pronounced signal changes in axial muscles, muscles of the anterior compartment in the lower limbs and extensor muscles in upper limbs. Patient 3 has a mild phenotype and an asymmetric distal involvement of leg muscles, confirmed by imaging. Patient 4 had an onset of distal weakness at age of 6 and developed cervical muscle weakness and kyphoskolioses, which stabilized at the age of 18. Muscle biopsies showed type 1 atrophy and multi/minicores in patient 1, type 2 predominance in patient 2 and fiber type disproportion in patient 4, confirming the heterogeneous and nonspecific nature of muscle histology findings in LDM. This report highlights early axial findings with head drop and kyphoscoliosis associated with proximal domain mutations of the MYH7 gene and also illustrates how mosaicism of one of such mutations can give rise to a milder and asymmetric presentation.

Laing myopapthy, axial involvement, mosaicism

Distal myopathies- #2619

P07- 98- GNE myopathy: clinical presentation, mutation analysis and longitudinal observations from a Global Patient Registry study

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GNE myopathy is an ultra-rare autosomal recessive distal myopathy caused by mutations in the GNE gene resulting in reduced sialic acid synthesis. Clinical presentation varies from asymptomatic carriers to severely debilitating forms. The aim of the analysis is to describe clinical presentation and progression of GNE myopathy using data collected via the GNE Myopathy Disease Monitoring Program (GNEM-DMP). The GNEM-DMP includes a hospital based/clinician reported natural history study and a global online patient self-reported registry. As of October 2015, 126 patients from 26 countries completed registry questionnaires including medical history, validated and non-validated health related questionnaires. In total 29 different GNE mutations were reported. Most of mutations 26/29 are missense and 3/29 are deletions with the frame shift. Clinical presentation at the onset most commonly included distal leg weakness (mean age 28.9), then progress to weakness in hands, difficulty climbing stairs, muscle spasms, twitching and pain (mean age 31.8), followed by difficulty sitting unaided, turning in bed and first indications to use a wheelchair or scooter (mean age 35.5). Lung function and cardiac function is compromised in 8.7% and 7.1% cases respectively. Pain (neck, shoulders, back and legs) was reported at an unexpectedly high rate -31.7%. Longitudinal observation was done using a Functional activity scale questionnaire (GNEM-FAS). From baseline to month 6, the most significant decrease in function was observed in the self-care domain (12.3%, n=15). Motor function and upper extremity domain score showed a very slight change. Longitudinal observations from the GNE myopathy DMP are continuing. A high rate of pain and perceived drop in self-care ability suggest that better pain management and involvement of a social care provider could be beneficial in management of patients with GNE myopathy.

GNE myopathy, distal myopathy, HIBM, Nonaka disease, QSM, DMRV

Distal myopathies- #2901

P07- 99- A recessive TTN founder mutation is causing a distal myopathy phenotype in a Serbian patient cohort

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Through whole exome sequencing we identified a recessive titin (TTN) mutation in 14 patients of Serbian ancestry with a distal or proximodistal myopathy. Three patients were homozygous for this nonsense TTN mutation (c.107635C>T; p.Gln35879Ter; NM_001267550.1) and eleven compound heterozygous. They shared a common core haplotype of 5Mb indicating a founder allele. This variant was absent from a population of Serbian healthy controls (n=103). In patients with compound heterozygous status, other TTN mutations consisted of: 5 frameshift (with same mutation detected in 3 patients), 4 nonsense, 1 essential splice site and 1 missense mutation. Nine patients were female (64%) and five male (36%) with the average age at the time of last examination of 36.8±10.9 years. Onset of age varied from 14 to 40 years, and most of the patients remained ambulant throughout the observation period. The clinical presentation associated with the mutation was fairly uniform, with predominant lower limb involvement and prominent weakness of distal muscles, especially the ankle and toe dorsiflexors. Patients showed mild to moderate proximal leg weakness. Distal muscles of the arms were only affected mildly in 3 patients, but mild scapular winging and mild shoulder girdle weakness was present in two thirds of them. Wasting of the lower limb muscles was most prominent in the anterior compartment of the lower legs and in the hamstrings, but generalized in patients with a longer disease course. There was no facial or bulbar weakness or respiratory involvement, and only one patient had cardiomyopathy. Serum CK levels were normal to mildly elevated. The patients with homozygous mutations did not show significant clinical differences compared to the compound heterozygous patients. Muscle MRI findings in 7 and muscle biopsy findings in 6 patients were compatible with a titinopathy and will be presented. Previously, muscular dystrophies caused by mutations in this extreme C-terminus of TTN (autosomal dominant tibial muscular dystrophy (TMD) and autosomal recessive LGMD2J) have been described primarily in Finland. The Serbian TTN founder mutation explains a sizable portion of distal myopathy patients in this region and may represent the most common single cause of distal myopathies in Serbian population.

titin, founder mutation, WES, autosomal recessive

Distal myopathies- #3018

P07- 100- LDB3-mutation in a family with distal muscle weakness

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Slowly progressive distal muscle weakness raises a differential diagnosis between hereditary motor polyneuropathies and distal myopathies, both groups of genetically heterogeneous disorders.

We present a family with three affected sibs displaying distal muscle weakness debuting in late adulthood in absence of sensory abnormalities or pyramidal tract signs. Initial nerve conduction studies in the propositus were compatible with a distal pure motor neuropathy. MRI imaging of muscle revealed fatty infiltration of the anterior tibial muscle, a muscle biopsy of the right gastrocnemius muscle showed minimal neurogenic features. Extensive genetic screening for mutations in known neuropathy genes was unremarkable.

The other two affected siblings were clinically evaluated ten years later and in addition to chronic neurogenic changes the needle EMG also revealed myogenic changes. MRI studies in two patients at that time showed a similar distal pattern of muscle involvement. In parallel, whole exome sequencing was performed in the index patient and revealed two missense alterations in LDB3 (p.Thr350Ile and p.Ala371Thr) of which only p.Ala371Thr segregates with the disease in the family. Muscle biopsy of the quadriceps in the index patient revealed pronounced variability of fiber diameters, increased numbers of internalized nuclei and limited signs of necrosis and myophagia. Limited numbers of flattened or angular atrophic fibers were observed. In addition large numbers of rimmed vacuoles were noted. Immunohistochemistry revealed the accumulation of ?B-crystalin and desmin and focally reduced staining for telethonin and nebulin. Electron microscopy revealed extensive myofibrillar alterations. Clinical and histopathological features strongly suggest the diagnosis a myofibrillar myopathy with a distal phenotype, matching best the description of the Markesbery-Griggs distal myopathy. Genetically, the segregating p.Ala371Thr variation in LDB3 is predicted to be a more benign variant than the p. Ala371Thr that is only found in the index patient. Further genetic and functional validation is ongoing as well as additional morphological studies in the other affected family members.

The current report illustrates the difficulty of differential diagnosis in patients with distal weakness and normal sensation. Our findings potentially extend the clinical and genetic spectrum of myofibrillar myopathies, in particular that of Markesbery-Briggs distal myopathy.

Myofibrillar myopathies, Next generation sequencing, Zaspopathies

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Myofibrillar myopathies- #2480

P07- 101- Exome sequencing identifies variants in two genes encoding the lim-proteins n-rap and fhl1 in a bag3 myofibrillar myopathy.

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Myofibrillar myopathies (MFMs) are a group of inherited or sporadic neuromuscular disorders with clinical and genetic heterogeneity, characterized by disintegration of Z-disks and myofibrils. The characteristic degradation of myofibrils is followed by ectopic accumulation of myofibrillar degradation products and ectopic accumulation of multiple proteins in the abnormal fiber regions. The clinical phenotypes include limb-girdle muscular dystrophy, distal myopathy, scapuloperoneal syndrome or rigid spine syndrome. Most patients with MFM present progressive muscle weakness but in some patients cardiomyopathy may precede this condition. MFMs have been associated with mutations in genes encoding Z-disk or Z-disk-related proteins. The c.626 C>T (P209L) mutation in BAG3 gene has been described as causative of MFM. BAG3 protein belongs to the BAG co-chaperon family and it is involved in major biological processes, such as apoptosis, protein quality control and autophagy as well as cytoskeleton organization. Moreover, BAG3 protein appears to be important for maintenance of mature skeletal muscle, altough a direct BAG3 role in muscle function has not yet fully elucidated. In this work, we aimed to further investigate the genetic basis of BAG3 MFM with whole exome sequencing (WES).

A MFM female patient carrying the c.626 C>T (P209L) mutation in BAG3 gene and her unaffected parents and brother were studied with WES. Quantitative Real Time PCR, immunohistochemistry and Western Blot analysis were performed to describe mRNA and protein pattern of expression of the identified genes.

Besides the known mutation in BAG3, the patient carried variants in N-RAP and FHL1 genes that encode muscle specific LIM domain containing proteins. These variants are associated with a decreased expression of NRAP and accumulation of FHL1 in aggregates in the patient's skeletal muscle tissue. Molecular dynamic analysis of the mutated FHL1 domain suggests a modification of its surface charge, which could explain FHL1 accumulation in muscle fibers.

To our knowledge this is the first study reporting the simultaneous presence of genetic variants in three genes possibly causative of MFM: BAG3 and FHL1, already independently associated to MFMs, and NRAP linked for the first time to MFM.

Myofibrillar myopathies, Exome sequencing, LIM proteins

Myofibrillar myopathies- #2672

P07- 102- Mutational spectrum and phenotypic variability of VCP related neurological disease in the UK

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Background: IBMPFD (OMIM number 167320), or hereditary inclusion body myopathy associated with Paget's disease of the bone and frontotemporal dementia is a rare autosomal dominant disorder due to mutations in the valosin-containing protein gene (VCP). VCP is a ubiquitous protein member of the AAA+ (ATP-binding proteins) protein family involved in multiple cellular functions.
Objective: To describe the clinical, pathological, and genetic findings of 42 patients from 21 families with IBMPFD diagnosed since 2009 in the UK.

Methods: Patients with genetically confirmed IBMPFD were identified at the Newcastle MRC Neuromuscular Centre and the clinical details, muscle biopsy findings and muscle MRI data were collected retrospectively.

Results: We estimate a point prevalence of the disease for the UK of 0.066/ 100 000 population. Muscle weakness was the leading symptom in 92.3% of the patients, either with a limb-girdle pattern and/or distal weakness. One patient presented with Paget disease of the bone and 3 mutation carriers were asymptomatic at the time of investigation. The mean age at onset was 42.8 years and the mean time to loss of ambulation 13.37 years. Parkinson's disease, bladder, anal, and erectile dysfunction were additional features. Two patients required assisted ventilation and four patients developed cardiomyopathy. Dementia or mild cognitive impairment was observed in 48.2% and Paget disease of the bone was present in 20.5% patients. All muscle biopsies showed myopathic changes, 61% had rimmed vacuoles and 33.3% small inflammatory infiltrates. We have identified four previously described missense mutations (p.R155C, p.R155H, p.R191Q, and p.R93C) and 2 novel mutations (p.G202W and p.A439G).

Conclusions: IBMPFD is a rare disorder probably under diagnosed due to the variable phenotype. Our study provides strong evidence that IBMPFD should also be considered in patients presenting with distal muscle wasting and weakness which is uncommon in other myopathies. Larger cohorts are needed to better clarify the phenotype and to establish phenotype/genotype correlations in order to produce clear guidelines for the diagnosis and management of patients with IBMPFD.

IBMPFD, Inclusion Body Myopathy with Early-Onset Paget Disease and Frontotemporal Dementia, valosin-containing protein, VCP gene mutations, prevalence

Myofibrillar myopathies- #3016

P07- 103- Extensive muscle biopsy retrospective analysis in a large cohort of Myofibrillar myopathies (MMF) patients

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Myofibrillar myopathies (MFM) are clinically and genetically heterogeneous conditions characterized by the presence of focal dissolution of the myofibrils associated with deposits of different proteins in skeletal muscle.
Mutation in DES (desminopathy), CRYAB (?B-crystallinopathy), MYOT (myotilinopathy), LDB3 (zaspopathy), BAG3 and FLNC (filaminopathy) have been associated to these conditions.
In this study we retrospectively analyzed clinical, morphological, immunocytochemical and ultrastructural findings of 39 MMF patients.
23 patients were male and 16 were female. Age at onset varied from 2 to 66. The most common clinical sign was distal weakness (66% of patients) followed by distal and proximal weakness (49%). CK level varied from normal to 1248 UI/L. Cardiac involvement was present in 20% of patients. Ten patients received a genetic diagnosis. DES was mutated in 5 patients, ZASP in 4, MYOT, BAG3 and FLNC in one patient respectively.
A muscle biopsy performed in all patients between 28 and 71 years showed the presence of irregularly stained eosinophilic masses, darkly stained with the mGT and lacking oxidative activity, associated with variable unspecific histological findings. The aggregates were variably positive for desmin, myotiline and ?B-crystallin in 87% of biopsies.
Ultrastructural analysis was performed in 19 patients and revealed: a) Inclusions or aggregates (rods, tubular filamentous aggregates and cytoplasmic bodies; b) Rimmed and/or autophagic vacuoles; c) Poorly defined areas of sarcomeric disorganizations.
We described a wide histopathological spectrum associated with MMF. Extensive immunohistochemical and immunofluorescense studies will help to better characterize our genetically undiagnosed MMF patients.

Protein aggregates myopathies, Myofibrillar myopathies, MMF, distal weakness

P08- Dystrophinopathies (Duchenne, Becker, others)- N° 104 to N° 156

Dystrophinopathies (Duchenne, Becker, others)- #2311

P08- 104- The natural history of Duchenne Muscular Dystrophy with corticosteroids using the Motor Function Measure

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