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**Mediterranean Society of Myology**
**and**
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***Founders: Giovanni Nigro and Lucia Ines Comi***

Three-monthly



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ORIGINAL ARTICLES

# Novel mosaic mutation in the dystrophin gene causing distal asymmetric muscle weakness of the upper limbs and dilated cardiomyopathy

Joana Ribeiro[1], Olinda Rebelo[1], Ana Fernández-Marmiesse[2] and Luís Negrão[1]

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**A group of heterogeneous muscle diseases are caused by dystrophin gene (*DMD*) mutations. We hereby present a male patient with a diagnosis of symptomatic dilated cardiomyopathy at 44 years-old who developed, soon after, weakness of distal right upper limb. At the age of 58, neurological examination revealed severe atrophy of right thenar muscles, flexion contractures on the right elbow, wrist and fingers, bilateral calf hypertrophy, myotatic areflexia in the upper limbs and hyporeflexia in the lower limbs. Manual muscle examination showed distal weakness of right upper limb muscles, severe on abductor pollicis brevis and extensor pollicis longus, and milder on interossei, finger extensors and brachioradialis muscles. Further testing revealed CK of 1500 U/L, a myopathic pattern on electromyography, and myopathic changes on right deltoid muscle biopsy, with immunohistochemistry showing focal sub-expression of dystrophin. Cardiac workup revealed a severe reduction in left ventricular ejection fraction, with a left ventricle of increased dimensions and global hypo-contractibility. A next-generation sequencing based panel for muscular diseases was performed and a nonsense mutation (c.C7525T) was identified in exon 51 of *DMD* gene, present in 70% of the gene readings (consistent with mosaicism).**

**Key words:** dystrophin gene, dilated cardiomyopathy, next generation sequencing

## Introduction

The dystrophinopathies comprise a spectrum of different muscular phenotypes, with variable involvement of skeletal and cardiac muscle (1). The mildest end of the spectrum includes the phenotypes of asymptomatic hyper-CK, while the severe end includes Duchenne muscular dystrophy (DMD) and DMD-associated dilated cardiomyopathy. Becker muscular dystrophy (BMD) in the middle spectrum of clinical severity of dystrophinopathies, together with DMD, present cardiac involvement – in DMD it is a late feature in the disease course, whilst in BMD it can be the presenting and most disabling feature (2, 3).

The dystrophinopathies result from mutations in the *DMD* gene located in the X-chromosome (Xp21.2-p21). Clinical phenotype can be predicted in most patients by the reading-frame rule. Out-of-frame mutations cause absence of dystrophin expression in muscle originating a severe DMD phenotype, whereas in-frame mutations result in a milder BMD phenotype (2, 3). The most frequent mutations are deletions and duplications, while point mutations are responsible for 25% of the genetic changes in the gene (4).

We hereby present a patient with distal asymmetric weakness of the upper limbs and dilated cardiomyopathy, caused by a novel somatic mosaic mutation in the *DMD* gene.

## Clinical findings

The patient was a Portuguese male, aged 58 years-old, born from a non-consanguineous couple. His family history was positive for coronary heart disease in his elder sister, due to proven atherosclerotic heart disease.

He had a personal history of type 2 diabetes mellitus, essential hypertension, dyslipidaemia and paroxysmal atrial fibrillation. At the age of 44, after an event of precordial pain, a symptomatic dilated cardiomyopathy was diagnosed. It was initially managed with medical treatment but, due to its symptomatic progression reaching

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New York Heart Association class IV, a cardiodisfibrillator was implanted at age 57. He is currently on medication for cardiac insufficiency and comorbidities, including diuretics, anti-arrhythmics, oral anticoagulants, and oral glucose-lowering agents.

He was evaluated in the neuromuscular disease unit because of weakness of the distal right upper limb beginning soon after the diagnosis of dilated cardiomyopathy. He did not complain of muscle cramps or myoglobinuria. Neurological examination revealed flexion contractures of the right elbow, wrist, thumb and 2nd, 3rd and 4th fingers (Fig. 1), and severe atrophy of thenar eminence muscles. Bilateral calf hypertrophy was present. Manual muscle strength examination of the right upper limb (graded according to MRC scale) showed weakness of the abductor pollicis brevis and extensor pollicis longus muscles (grade 0/5), interossei muscles (grade 3–/5), and finger extensors and brachioradialis muscles (grade 4/5 and 4+/5, respectively). In the left upper limb, only finger abduction was mildly impaired (grade 4/5). Tendon reflexes were absent in the upper limbs and diminished in the lower limbs. Cranial nerves, sensory examination and gait were unremarkable.

## Complementary exams

A transthoracic echocardiography revealed a severe global left ventricle (LV) systolic dysfunction, with global hypo-contractility and severely compromised LV ejection fraction, and moderately compromised systolic function of right ventricle; radionuclide cardiac angiogram showed a global LV ejection fraction of 24%, with a LV of increased dimensions and global hypokinesia. Cardiac angiography did not show signs of coronary disease. An evaluation of respiratory function revealed a moderate restrictive syndrome (64.6% of predicted forced vital capacity), with normal alveolocapillary diffusion study.

Laboratory workup revealed an elevated BNP of 948.8 pg/mL (upper reference value 100 pg/mL), and hyper-CK of approximately 1500 U/L (upper reference value 171 U/L).

Electromyography showed a myopathic pattern, with normal motor and sensory nerve conduction studies.

*Muscle biopsy*

Right deltoid muscle biopsy revealed a myopathic pattern, with fibres of different sizes, internalized nuclei, and rare necrotic fibres (Fig. 2A-B). No fibrosis or fatty replacement was present. Careful re-evaluation of the immunohistochemical staining after molecular studies revealed focal sub-expression of dystrophin with Dys1, Dys2 and Dys3 antibodies (Fig. 2C). In this patchy pattern of dystrophin expression, the majority of fibres still showed normal dystrophin labelling.

*Molecular studies*

A next generation sequencing panel for muscle diseases was performed through a custom targeted next generation sequencing panel, followed by Sanger sequencing validation of the identified mutations. This study revealed a nonsense novel mutation (c.C7525T) in exon 51 of the *DMD* gene in somatic mosaicism. Only 70% of X chromosomes from the patient carried the mutation (Fig. 3). This previously undescribed variant predicts a stop codon (p.Gln2509*). This variant was not registered in 1000 genomes, Single Nucleotide Polymorphism (dbSNP) databases, or in the Leiden Open Variation Database (LOVD) associated to disease. It was not detected in 401 chromosomes analysed from the Iberian population. Since this variant was not found

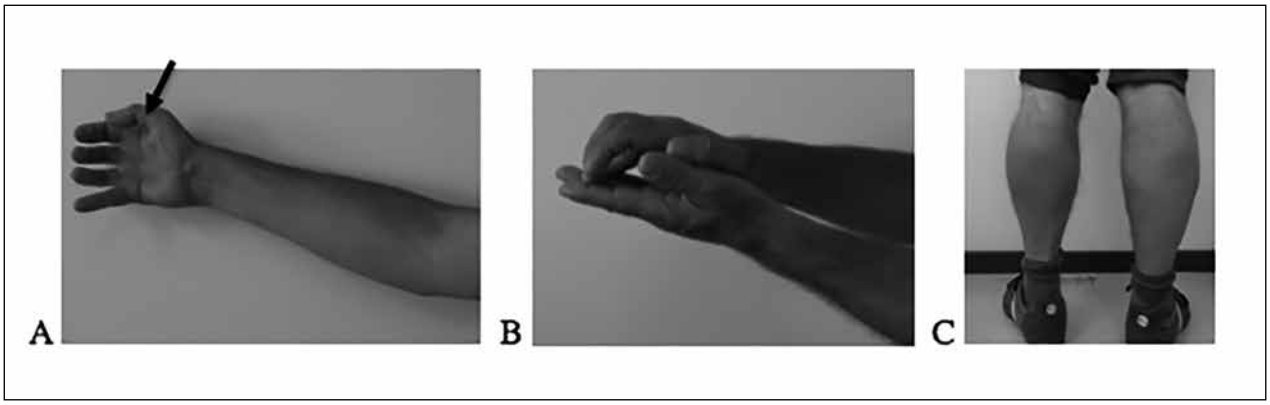


**Figure 1.** Atrophy of the right thenar eminence (arrow) and flexion contracture of the right elbow (**A**); Flexion contractures of the right wrist and fingers (**B**); Calf hypertrophy (**C**).

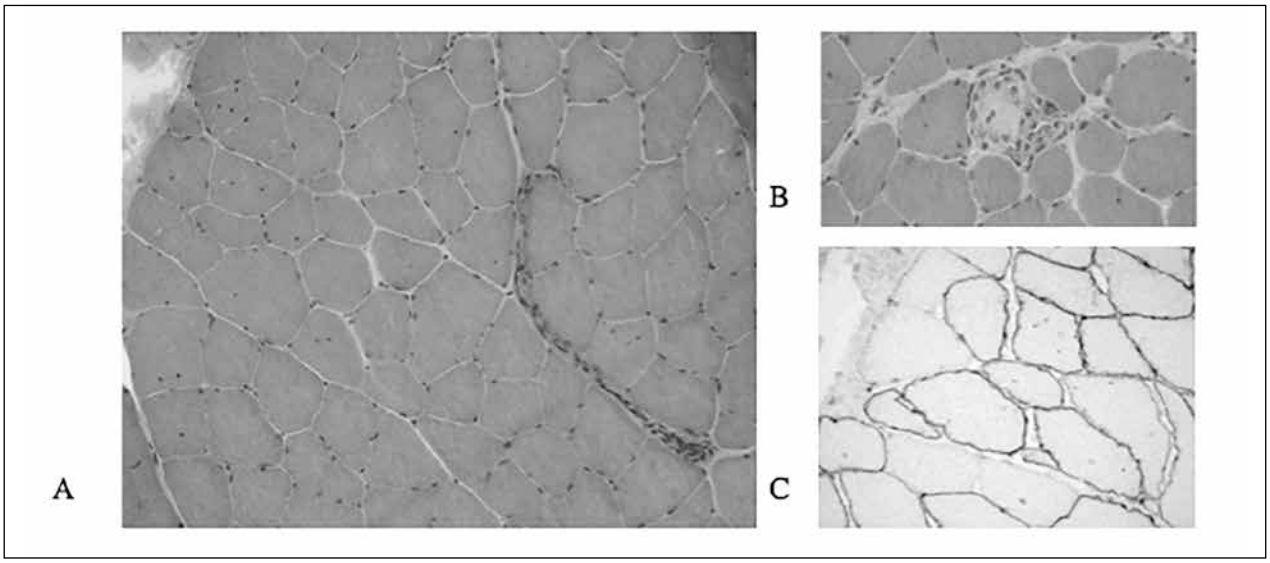


**Figure 2.** Deltoid muscle biopsy. Increased variability in fibre size and rare necrotic fibres (H&E - 200x) (**A**, **B**); Immunohistochemical staining for Dys3 showing focal sub-expression of dystrophin (200x) (**C**).

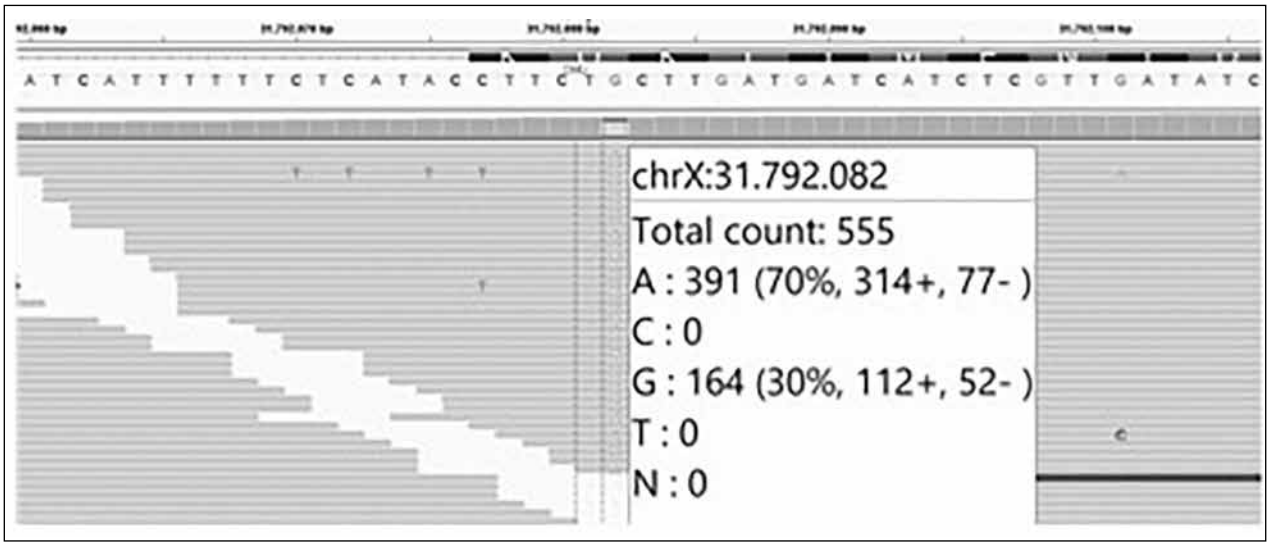


**Figure 3.** IGV image showing the variant found in the patient. Of the 555 reads reached for this nucleotide, 70% are carriers of the nonsense allele while 30% are carriers of the wild type allele.

in the control population and is a nonsense mutation, we consider it as likely pathogenic.

The patient had been previously tested (single-gene) for mutations in the *MYH7*, *FKRP* and *LMNA* genes, with a negative result.

## Family genetic testing

The proband's parents were already deceased, and the sister was not available for gene testing. The patient has two daughters, who were tested for *DMD* gene carrier status, and only the eldest daughter inherited the mutation. On neurological examination, she presented a mild calf hypertrophy without muscular weakness.

## Discussion

We present a male patient with a *DMD* gene mutation in somatic mosaicism, presenting a severe dilated cardiomyopathy and a predominantly distal, asymmetric upper limb muscular weakness.

We believe that both the myocyte and skeletal

muscle involvement are related to the novel mutation found – the former confirmed by the absence of coronary disease or other pathology causing cardiac failure, and the latter by the muscle biopsy, revealing a myopathic muscle with sub-expression of dystrophin.

The asymmetric involvement in *DMD* gene mutations has been previously described in female manifesting carriers in various proportions (5, 6), and in males harbouring somatic mutations in the *DMD* gene (including a hemi-atrophy pattern, mild muscular limb girdle weakness, and overt cardiomyopathy with minor muscle symptoms) (7-9). The genetic normalization process, where dystrophin-negative muscle is replaced by dystrophin-positive muscle as a function of age, was considered to mitigate muscular symptoms in some of this patients and the predominantly cardiac phenotype (9). We propose that this could account for both the late presentation of the muscular phenotype and its asymmetry in our patient.

However, the predominantly distal presentation of the muscular weakness is uncommon, and, to our knowledge, has never been described in males or female-carriers with *DMD* gene mutations. Although calf hypertrophy was present, there were no limb-girdle related complaints or weakness. Further studies involving genetic analysis of muscle dystrophin may help in clarifying the real expression and proportion of the normal and the abnormal dystrophin in the patient's skeletal muscle, especially if a more distal muscle is studied.

The typical transmission pattern for this X-linked disorder would be that all female descendants were carriers for the mutation. The atypical familial transmission presented is probably due to the fact that the patient is also a mosaic for germline cells (10).

This clinical case expands the genotype and phenotypic presentation of *DMD* gene mutations.

## Conclusions

We present a rare and very atypical phenotype of muscular involvement in a male patient with a novel *DMD* gene mutation in somatic mosaicism – asymmetric distal weakness of the upper limbs – associated with a severe dilated cardiomyopathy.

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# Long term history of a congenital core-rod myopathy with compound heterozygous mutations in the Nebulin gene

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**Mutations in the Nebulin gene (NEB) may cause core-rod myopathy. The large size of the gene so far prevented inclusion of its routine analysis by didesoxy resequencing methodology in the diagnostic regime for muscular dystrophy cases. Here we report a 54-year-old female with a rare histological myopathy presentation of co-occurring cores and rods. The patient reported early childhood onset weakness. Muscle-MRI showed mainly proximal muscle involvement. We identified two compound heterozygous non-sense mutations in NEB (c.19653G > A, p.W6551* exon 127 and c.25441C > T, p.R8481* exon 182) using a comprehensive next generation sequencing (NGS)-based approach named Mendeliome Sequencing. The p.W6551* mutation has not been reported elsewhere. Early diagnosis by NGS shall be chased since even a scoliosis surgery at the age of 18 years had failed to initiate a neurological workup. Rather, cosmetic surgery for facial weakness had been performed recently, albeit with an unsatisfactory outcome.**

**Key words:** core-rod myopathy, Nebulin, Mendeliome, muscle magnetic resonance imaging, cosmetic surgery

## Introduction

Mutations in giant genes like Titin (*TTN*) and Nebulin (*NEB*) have been described to cause congenital myopathy. Till recently, the sheer size of these large genes made it difficult to sequence larger cohorts of patients in order to decipher genotype-phenotype correlations. However, next-generation sequencing now enables us to uncover the underlying mutations. Congenital myopathies are primary muscle diseases of broad phenotypic and genetic heterogeneity. Two of the more common congenital myopathies, Central Core Disease (CCD) (1) and Nemaline Myopathy (NM) (2), are associated with unique structural characteristics in muscle fibers. Histology of biopsies from affected individuals revealed oxidative enzyme activity lacking central cores in CCD or rod shaped Nemaline bodies in NM. CCD typically manifests as an early-onset but non-progressive disease most frequently caused by pathogenic ryanodine receptor 1 (*RYR1*) mutations (3, 4). Limb girdle and axial muscles are predominantly involved in core myopathies. Orthopedic complications such as hip dislocation, scoliosis, and foot deformities are also often found in CCD. NM is clinically and genetically more heterogeneous, ranging from severe fetal akinesia to adult-onset mild weakness, with causative mutations described in 10 genes involved in thin filament structure (*MYPN, NEB, ACTA1, TPM2, TPM3, TNNT1, CFL2, LMOD3*) (5) or ubiquitin pathway (*KBTBD13, KLHL40, KLHL41*). Nebulin (*NEB*) mutations, the most frequent cause of NM, account for ~50 % of cases (6). This large, 183-exon-spanning gene encodes a critical component of sarcomere thin filament assembly, regulating minimum filament length (7) and contractile force (8, 9). Large parts of the protein are comprised of repetitive 35-mer modules, containing an actin binding site, and super repeats of seven modules, containing a motif with putative tropomyosin binding ability (10). Patients with NEB mutations present with facial weakness, nasal speech, and dysarthria frequently. Sanger sequencing of Nebulin (11) is complicated by the large size and highly repetitive sequence of the gene, thus the screen-

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ing of large cohorts was not feasible in the past. Therefore, many patients with NM were not genetically characterized in the past, which in turn resulted in an under-evaluation of this genotype-phenotype correlation in myopathy patients. We here applied a comprehensive screening panel for clinically significant genes, called the Mendeliome (12, 13), in a patient suffering from a myopathy featuring both cores and rods in muscle fibres for over 50 years, revealing compound heterozygous mutations in the Nebulin gene. We present the long-term disease course of a Nebulin-related Nemaline myopathy.

## Material and methods

*Patient*

This is a case report of a patient in clinical follow-up at the Department of Neurology, University Hospital Cologne. The patient consented for publication of the clinical information. The genetic study was approved by the local institutional review board of the University Hospital Cologne and informed consent for genetic work-up was obtained from the patient and family members.

*Genomic analysis*

We used targeted gene sequencing on the Illumina Trusight One panel, (Illumina, San Diego, CA, USA) providing comprehensive coverage of 4.813 clinically relevant genes, a technique also called Mendeliome Sequencing (MS) (further details see supplementary material page 127) (13, 14).

*Neuropathology*

The biopsied left deltoid muscle tissue was snap-frozen in isopentane (Fluka, Neu-Ulm, Germany), precooled in liquid N2 immediately after biopsy, and stored at – 80°C (15). Muscle biopsy work-up methods are presented in the supplementary material (page 127).

*Muscle magnetic resonance imaging (MRI)*

Muscle MRI of the lower limb was performed using conventional T1-, T2-, and STIR-weighted spin echo. Non-contrast images were obtained from pelvis, thighs, and legs.

## Results

*Case presentation*

This 54-year-old female was referred because of general weakness, difficulty in climbing stairs, and stress dyspnea. Symptoms had been present since early childhood, and she reported that she had been slower in walking and running than her peers during childhood. She developed scoliosis in early adolescence and underwent stab osteosynthesis surgery at the age of 18 years. Furthermore, the patient had cosmetic surgery a few years before being referred to us due to bilateral ptosis. The family history was unremarkable for neuromuscular diseases. On clinical examination at referral, she had a myopathic face, high-arch palate, nasal speech, and right-sided tongue atrophy with deviation to the right. Weakness was prominent at distal muscles of upper limbs and proximal muscles of lower limbs. Substantial weakness was also noted at neck flexor muscles and axial muscles, which resulted in an inability to rise from supine position with positive Gowers' sign. However, the patient was able to walk without any help. Deep tendon reflexes were equal at both sides, and sensory system was intact. Serum studies demonstrated a slightly elevated creatine kinase (CK) level of 428 U/L. Serum lactate levels were normal. Electromyography (EMG) showed sparse pathological spontaneous activity, small polyphasic potentials, early density interference, and occasional pseudomyotonic discharges. Subsequently, a muscle biopsy was performed from the left deltoid muscle.

*Muscle magnetic resonance imaging*

MRI of the lower limbs revealed predominant proximal muscle involvement (Fig. 1B). Within the thigh, the ischiocrural and medial muscles showed fatty atrophic changes with the semimembranosus muscles being mostly affected, whereas the anterolateral and the lower leg muscles revealed only minor changes in signal intensity without any selective involvement.

*Histopathology*

A deltoid muscle biopsy showed variable fiber sizes and increased internalization of nuclei on H&E staining (Fig. 2A). Modified Gomori trichrome staining revealed fuchsinophilic rods in most of the fibers (Fig. 2B, C). NADH staining showed numerous cores with absent enzyme activity in several fibers (Fig. 2D) while mATPase staining was inconspicuous (Fig. 2E). Toluidine blue staining detected especially rods and single cores on longitudinal sections (Fig. 2F). The presence of rods and cores was confirmed by electron microscopy (Fig. 3A-C). Up to 5 µm long rods could be identified, preferentially around nuclei. Numerous muscle fibers harbored core-like disintegration of myofibrils associated with the breakup of Z bands, enlargement of many muscle fiber mitochondria and contained paracrystalline inclusions; several muscle fiber nuclei showed prominent lobulation (Fig. 3D). The mitochondrial and myonuclear alterations have been considered secondary and unspecific.

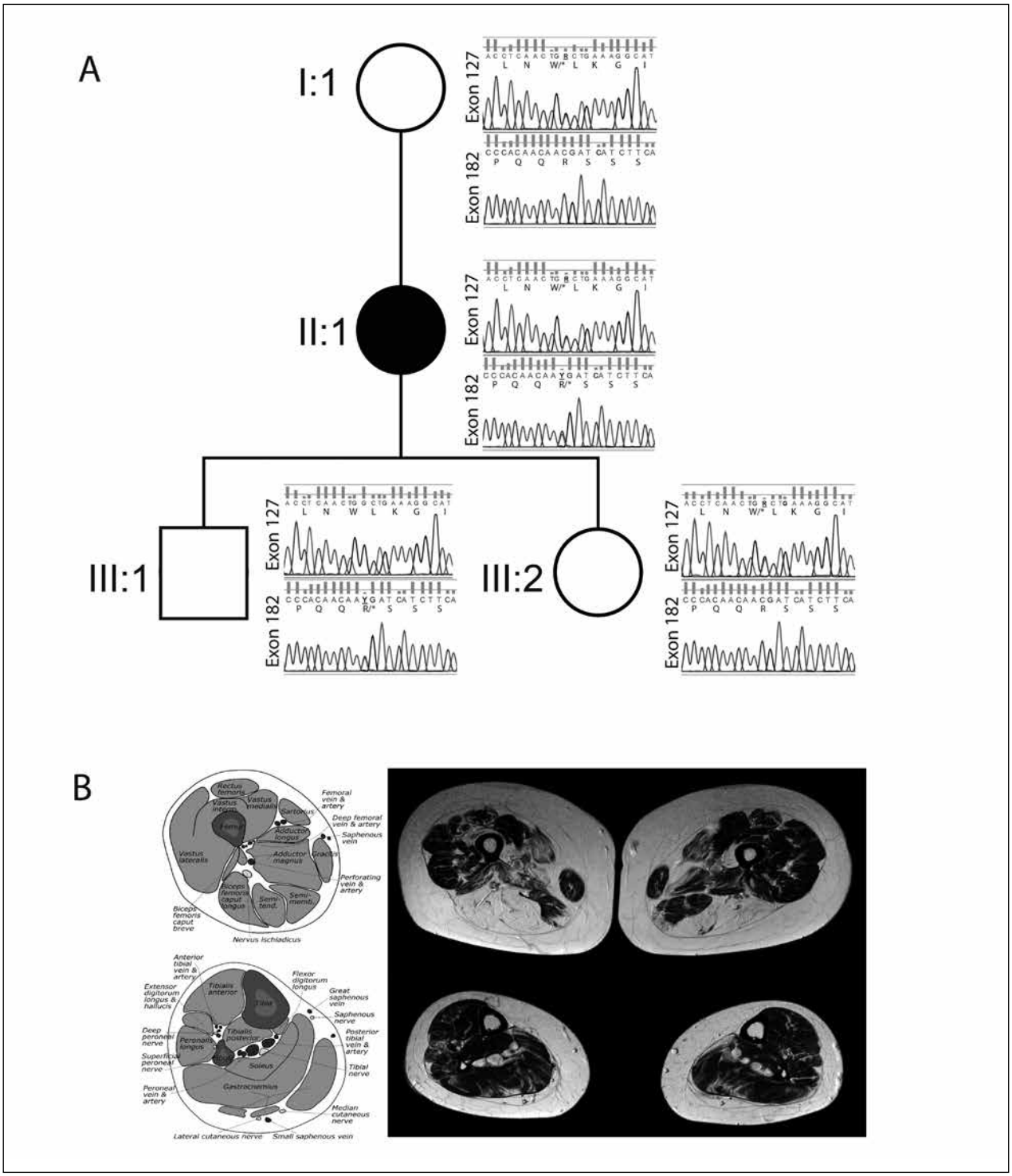


**Figure 1.** Pedigree of the patient (II:1) shows two heterozygous frameshift mutations in the nebulin (NEB) gene c.19653 G > A in exon 127 causing p.W6551* and c.25441 C > T in exon 182 causing p.R8481*. The bioinformatics analysis showed that the aberrant amino acid changes are located on the super repeats (S15-S21) and serine-rich domains of the protein. The variants were confirmed by Sanger sequencing, which revealed that the mother (I:1) and the daughter (III:2) have a recessive allele in exon127 (p.W6551*). Furthermore, the son (III:1) has a recessive allele in exon 182 (p.R8481*). The mother and the children were clinically unaffected (**A**). Muscle magnetic resonance imaging of the lower limbs showing predominant proximal involvement, within the thigh the ischiocrural and medial muscles shows fatty atrophic changes (**B**).

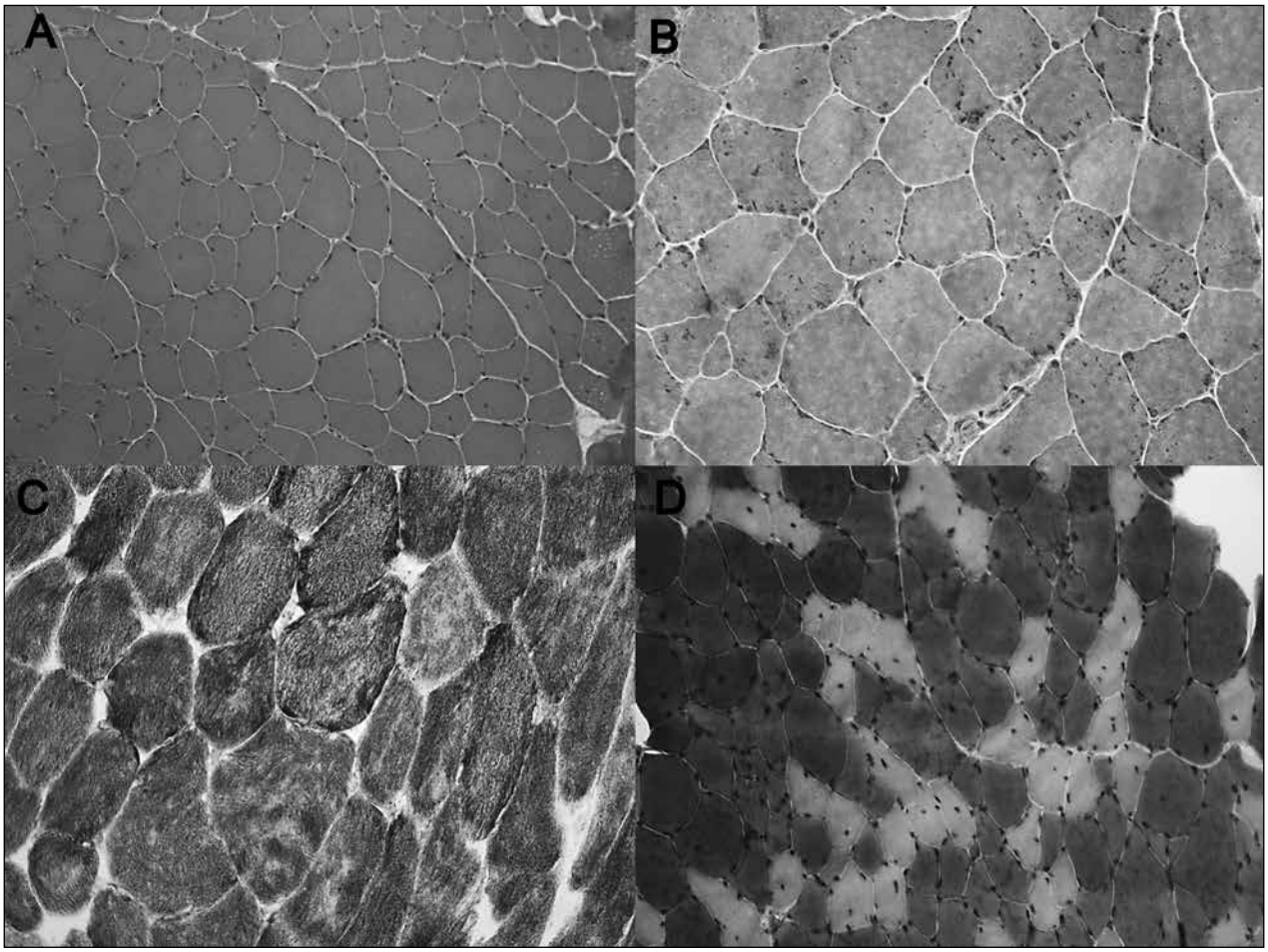


**Figure 2.** Muscle biopsy showed variation in fiber size and increased internalization of nuclei on H&E staining (**A**). Modified Gomori trichrome staining revealed fuchsinophilic rods in most of the fibers (**B**). NADH staining showed numerous cores with absent enzyme activity in several fibers (**C**), while mATPase staining was inconspicuous (**D**).

*Genetic results*

Mendeliome sequencing revealed two heterozygous frameshift mutations in the Nebulin (NEB) gene c.19653G > A in exon 127 causing p.W6551* and c.25441C > T in exon 182 causing p.R8481* according to NM_001271208.1 (Fig. 1A). The p.R8481* allele was detected in 6/120725 population chromosomes by the Exome Aggregation Consortium (http://exac.broadinstitute.org), 10/276544 heterozygous alleles in the gnomAD server (http://gnomad-beta.broadinstitute.org), the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar) accession number is 449500 and was also reported earlier by Lehtokari et al. (6). The clinical significance is reported as pathogenic for this mutation (https://www.ncbi.nlm.nih.gov/clinvar). But the p.W6551* mutation was not reported in the Exome Variant Server, gnomAD, ClinVar and 1000 genomes databases. Arginine at 8481 and Tryptophan at 6551 are conserved in vertebrates (16).

## Discussion

This case presents the long-term disease course of core-rod-myopathies revealing compound heterozygous stop-mutations in the Nebulin gene. The p.W6551* is a novel mutation, not described in the literature to our knowledge. The p.R8481* mutation in compound heterozygosity with another more proximal frameshifting mutation p.Ser2820fs was reported earlier in a family with typical Nemaline myopathy features by Lehtokari et al., however lacking further clinical details (6). The combination of cores and rods as revealed by muscle biopsy has been described in a few NEB-related cases with both a severe form (17) and mild forms with normal strength in the leg muscles (6, 18).

The two truncating mutations (p.W6551* in exon 127 and p.R8481* in exon 182) are located in super repeats (S15-S21) and serine rich domains of the protein, respectively (19). The repeat domains have been shown to inter-

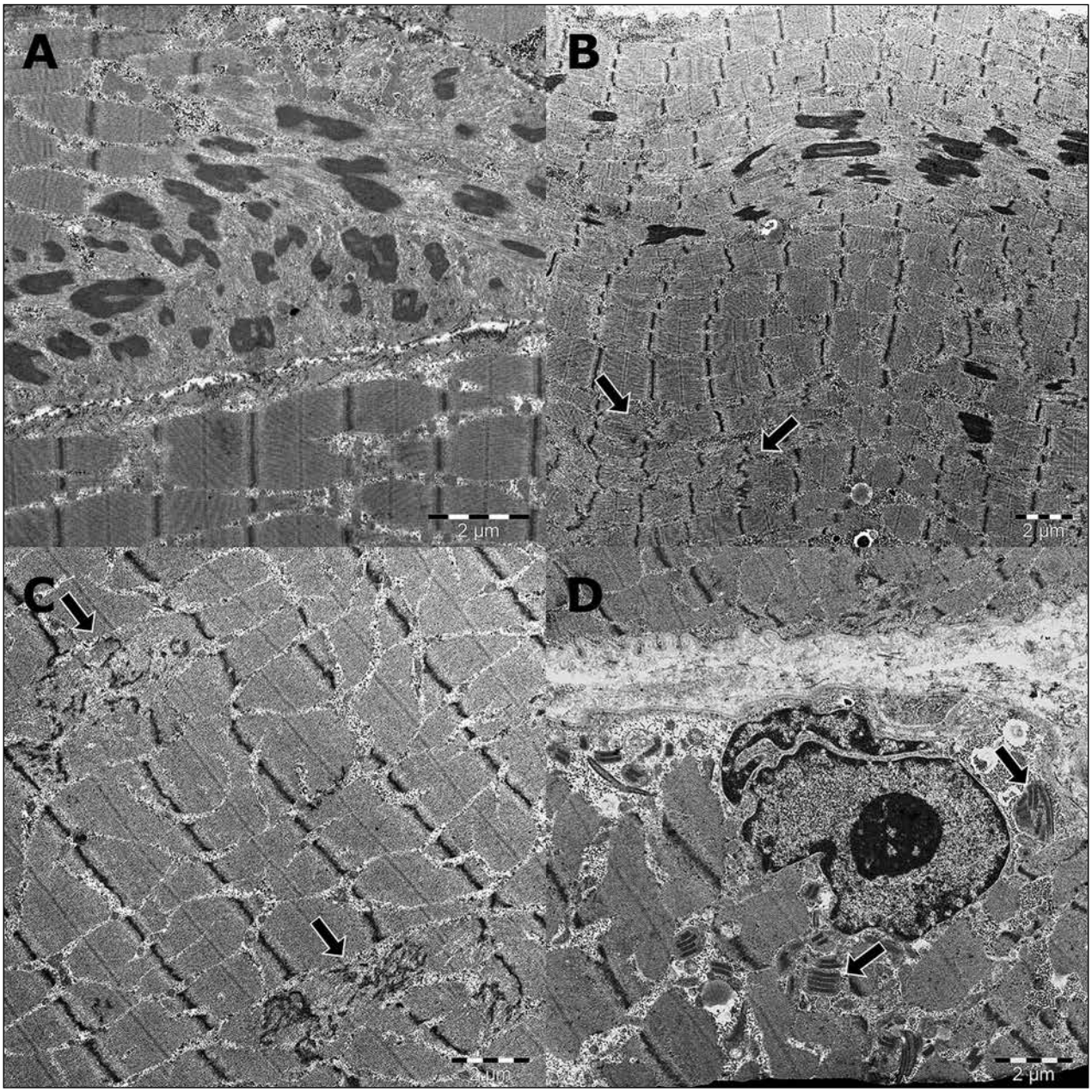


**Figure 3.** The presence of rods and cores were confirmed by electron microscopy, up to 5 µm long rods could be identified preferentially around nuclei. Numerous muscle fibers harbored core-like disintegration of myofibrils associated with breakup of Z bands (**A-C**). Many muscle fiber mitochondria were enlarged and contained paracrystalline inclusions, several muscle fiber nuclei showed prominent lobulation (**D**).

act with thin filament components, whereas C-terminal regions have unique sequences for binding to proteins at the Z-line. The serine-rich region at the C-terminal contains several predicted phosphorylation sites adjacent to a Src homology 3 (SH3) domain, which was shown to play a vital role in binding to titin and myopalladin (20).

The muscle biopsy represents a rod-core myopathy. The mitochondrial and myonuclear alterations revealed by electron microscopy were considered to be secondary and not specific. Unfortunately, no immunoblotting or immunohistochemistry was performed earlier for Nebulin and no frozen muscle biopsy was left over to perform these investigations. However, other publications show reduced levels of Nebulin in patients with truncating mutations compared to healthy controls (21). Thus, we may speculate that our further C-terminal stop mutation might

lead to a truncated Nebulin protein expression with reduced levels.

The muscle MRI of our case showed predominantly proximal involvement, whereas in previous reports an early and isolated involvement of the tibialis anterior muscle (22) or a predominant distal involvement (12) has been described as the most typical finding in NEB-related NM. A possible explanation for this discrepancy could be that corresponding to the expanding range of phenotypes and the identification of an increasing number of mutations in Nebulin, we are now uncovering the entire clinical spectrum and earlier have been underpowered to claim a specific MRI pattern.

The number of genes associated with congenital myopathies exceeds 20, including giant genes such as TTN with 363 exons, NEB with 183 exons, and RYR1 with 106 exons (23, 24). NGS technologies, which provide a more practical and cost-effective approach compared to conventional gene sequencing techniques, are now being widely implemented in the diagnosis of neuromuscular diseases.

Finally, this case illustrates that despite typical muscle pathology features the diagnosis of a structural myopathy was not made until the patient was 54 years old. Interestingly, even the operation (to correct for scoliosis) at the age of 18 did not trigger further neurological workup. The patient had already shown symptoms during childhood, a congenital form that is not compatible with an adult manifestation. Unfortunately, cosmetic surgery for ptosis and facial weakness was performed with a predictable unsatisfactory outcome.

## Acknowledgements

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# Supplementary Material

## Genomic Analysis

We used targeted gene sequencing on the Illumina Trusight One panel (Illumina, San Diego, CA, USA) providing comprehensive coverage of 4.813 clinically relevant genes, a technique also called Mendeliome Sequencing (MS) (1). The coverage was 118-fold i.e., 10x coverage for 98.1% of target sequences and 30x coverage for 93.8% of target sequences. The Cologne Center for Genomics VARBANK pipeline v.2.12 (https://varbank.ccg.uni-koeln.de/) was used for data analysis. Variants were filtered for dominant and compound heterozygous mutations, as well as reading quality and allele frequency among populations. Filtered functional variants in compound heterozygous inheritance were tested based on in silico prediction databases as described elsewhere (2).

## Muscle biopsy work–up

The biopsied left deltoid muscle tissue was snap-frozen in isopentane (Fluka, Neu-Ulm, Germany), pre-cooled in liquid N2 immediately after biopsy, and stored at -80°C. For enzyme histochemistry, 9 µm thick serial frozen sections were stained with hematoxylin and eosin (H&E), adenosine triphosphatase (mATPase, pH 9.4, 4.6, and 4.2), nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase (NADH TR), modified Gomori trichrome, and cytochrome oxidase (COX). Semithin section histology and preparation for electron microscopy were performed as described previously (3). For electron microscopy, glutaraldehyde-fixed muscle specimen was post-fixed with OsO4 1% in 0.1M cacodylate buffer containing 50 mM $K_3Fe(CN)_6$. Muscle specimen were embedded in epoxy resin. Ultra-thin sections were contrasted with uranyl acetate and lead citrate and, finally, examined with a Philips EM 400 T electron microscope.

## References

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# PROCEEDINGS OF THE XIII CONGRESS OF MEDITERRANEAN SOCIETY OF MYOLOGY

## Avanos, Turkey

## June 27-29, 2018


13th Meeting of the Mediterranean Society of Myology
in connection with the
2nd Congress of the Turkish Neuromuscular Society
27-29 June 2018
Avanos, Cappadocia, Turkey

**PROGRAM**

## ÇOCUK NÖROLOJİ NÖROMUSKÜLER HASTALIKLAR KURSU

### 26 HAZİRAN 2018 SALI

| | |
|---|---|
| 08:30 - 09:00 | Kayıt ve Açılış |
| 09:00 - 09:45 | Kas Biyopsisi<br>**Beril Talim** |
| 09:45 - 10:30 | Nöromusküler Hastalıklara Genel Yaklaşım ve Tedaviler<br>**Haluk Topaloğlu** |
| **10:30 - 11:00** | **Kahve Arası** |
| 11:00 - 11:45 | Duchenne/Becker Ve Diğer Musküler Distrofiler<br>**Özlem Hergüner** |
| 11:45 - 12:30 | Genetik Testler<br>**Derya Erçal** |
| **12:30 - 14:00** | **Öğle Yemeği** |
| 14:00 - 14:45 | Artrogiroposis<br>**Beyhan Tüysüz** |
| 14:45 - 15:30 | Motor Nöron Hastalıkları<br>**İlknur Erol** |
| **15:30 - 16:00** | **Kahve Arası** |
| 16:00 - 16:45 | Konjenital Myopatiler<br>**Haluk Topaloğlu** |
| 16:45 - 17:30 | Kas ve Sinirin Metabolik Hastalıkları<br>**Göknur Haliloğlu** |
| 17:30 - 18:30 | Vaka Sunumları |

## 27 HAZİRAN 2018 ÇARŞAMBA – SALON A

| | |
|---|---|
| 08:00 - 08:45 | Hipotonik Bebek<br>**Göknur Haliloğlu** |
| 08:45 - 09:30 | Konjenital Musküler Distrofiler<br>**Uluç Yiş** |
| 09:30 - 10:15 | Mitokondrial Hastalıklar<br>**Beril Talim** |
| **10:15 - 10:45** | **Kahve Arası** |
| 10:45 - 11:30 | Kasın Inflamatuar Hastalıkları<br>**Deniz Yüksel** |
| 11:30 - 12:15 | Herediter Periferik Nöropatiler<br>**İlknur Erol** |
| **12:15 - 13:30** | **Öğle Yemeği ve BİOGEN UYDU SEMPOZYUMU (SATELLITE SYMPOSIUM – BIOGEN)** |
| 13:30 - 14:15 | Sinirin Inflamatuar Hastalıkları<br>**Deniz Yüksel** |
| 14:15 - 15:00 | Myastenia Gravis<br>**Haluk Topaloğlu** |
| 15:00 - 15:45 | Nöromusküler Hastalıklarda Gelecek<br>**Mehmet Alikaşifoğlu** |
| **15:45 - 16:15** | **Kahve Arası** |
| 16:15 - 17:00 | Beslenme<br>**Hasan Özen** |
| 17:00 - 17:45 | Solunum<br>**Selman Kesici** |
| 17:45 - 18:30 | Nöromusküler Araştırmalarda Uygulanan Testler<br>**Ayşe Karaduman, Öznur Yılmaz** |

## 27 HAZİRAN 2018 ÇARŞAMBA – SALON B

| | |
|---|---|
| 09:00 - 09:30 | Spinal Musküler Atrofinin Klinik Ve Fonksiyonel Özellikleri<br>**Ayşe Karaduman** |
| 09:30 - 10:30 | Değerlendirmeler: CHOP-Intend<br>**Ayşe Karaduman, Numan Bulut** |
| **10:30 - 10:45** | **Kahve Arası** |
| 10:45 - 12:00 | HFMSE<br>**İpek Alemdaroğlu, Numan Bulut, Güllü Aydın** |
| **12:00 - 13:00** | **Öğle Yemeği** |
| 13:00 - 13:30 | DMD Klinik ve Fonksiyonel Özellikler<br>**Öznur Yılmaz, Numan Bulut** |
| 13:30 - 15:30 | Vakalarla DMD'de Fizyoterapi ve Rehabilitasyon<br>**Ayşe Karaduman, Öznur Yılmaz, İpek Alemdaroğlu** |
| **15:30 - 15:45** | **Kahve Arası** |
| 15:45 - 16:30 | Günün Özeti ve Tartışma<br>**Ayşe Karaduman, Öznur Yılmaz, İpek Alemdaroğlu** |

## SCIENTIFIC PROGRAMME

### 27 JUNE 2018, WEDNESDAY

| | |
|---|---|
| **19:00 - 19:20** | **Welcoming Lecture Followed by Reception**<br>Other side of Cappadocia: "Run in Cappadocia"<br>**Aydın Ayhan Güney, Pınar Arpınar Avşar** |

### 28 JUNE 2018, THURSDAY

| | |
|---|---|
| 08:00-08:30 | OPENING OF CONGRESS<br>**Prof. Giovanni Nigro**, Eulogy by **Victor Dubowitz**, UK<br>**SESSION 1. GENETICS AND CLASSIFICATION OF LIMB-GIRDLE DYSTROPHIES**<br>**Moderators: Luisa Politano, Haluk Topaloğlu** |
| 08:30 - 09:00 | Classification and Pathophysiology<br>Marco Savarese, IT |
| 09:00 - 09:30 | The Gene Therapy Field in LGMD<br>Isabelle Richard, FR |
| 09:30 – 10:00 | Solve the Unsolved LGMDs: The Next Approach<br>Vincenzo Nigro, IT |
| 10:00 - 10:30 | Oculopharyngeal Muscular Dystrophy: From Bench to Bedside and Back Again<br>G. Butler-Browne, FR |
| **10:30 - 11:00** | **Coffee Break**<br>**SESSION 2. CLINICAL FEATURES OF LIMB-GIRDLE DYSTROPHIES**<br>**Moderators: Piraye Oflazer, Yehuda Shapira** |
| 11:00 - 11:30 | Clinical Features of Limb Girdle Dystrophies: an Overview<br>Jordi Diaz-Manera, SP |
| 11:30 - 12:00 | Metabolic Myopathies Mimicking Limb Girdle Dystrophy<br>Corrado Angelini, IT |
| 12:00 - 12:30 | Myofibrillar Myopathies<br>Duygu Selcen, USA and TR |
| 12:30 - 13:00 | Muscular Dystrophies with Mental Retardation<br>Haluk Topaloglu, TR |
| 13:00 - 14:00 | **Lunch, SATELLITE SYMPOSIUM - SAREPTA** |

28 JUNE 2018, THURSDAY

14:00 - 15:30 **ORAL PRESENTATIONS / OP1 – OP9**

**Modarators: Feza Deymeer, Vincenzo Nigro**

**OP1 SMN DEFICIENCY CAUSES UPREGULATION OF MICROTUBULE ASSOCIATED PROTEIN 1B (MAP1B) IN MODELS OF SPINAL MUSCULAR ATROPHY (SMA)**
GAMZE BORA [1], SEBASTIAN RADEMACHER [4], NIKO HENSEL [2], DILA KOYUNOĞLU [1], MERVE SUNGUROĞLU [1], PETER CLAUS [2], HAYAT ERDEM-YURTER [1]

**OP2 COMPARATIVE TRANSCRIPTOME ANALYSIS OF DISTINCT STROMAL CELL POPULATIONS DURING EXTRACELLULAR MATRIX REMODELING IN SKELETAL MUSCLE**
CANSU ÖZDEMİR [1], DUYGU AKÇAY [2], DIĞDEM YÖYEN ERMİŞ [3], EKİM TAŞKIRAN [4], GÜNEŞ ESENDAĞLI [3], ÇETIN KOCAEFE [2],

**OP3 PHOSPHORODIAMIDATE MORPHOLINO OLIGOMERS FOR TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY**
KATE MARESH [1], MAY TIET [2], MICHELA GUGLIERI [2], JOANA DOMINGOS [1], VOLKER STRAUB [2], THOMAS VOIT [1], FRANCESCO MUNTONI [1]

**OP4 NOVEL ANIMAL MODELS FOR SARCOGLYCANOPATHY**
CHIARA FECCHIO , MICHELA SOARDI , MARCELLO CAROTTI , DORIANNA SANDONà

**OP5 TARGETED SEQUENCING WITH EXPANDED GENE PROFILE ENABLES HIGH DIAGNOSTIC YIELD IN NON-5Q-SPINAL MUSCULAR ATROPHIES**
MERT KARAKAYA [1], ULUC YIS [2], BERTOLD SCHRANK [3], REZA MAROOFIAN [4], HALUK TOPALOGLU [5], PETER NUERNBERG [6], RAOUL HELLER [1], BRUNHILDE WIRTH [1]

**OP6 A COHORT OF CONGENITAL MYOPATHY PATIENTS FROM A TERTIARY NEUROMUSCULAR REFERRAL CENTER: DIAGNOSTIC YIELD FROM NEXT GENERATION SEQUENCING (NGS) TECHNIQUES**
DIDEM ARDICLI [1], MERT KARAKAYA [2], GOKNUR HALILOGLU [1], KRISTEN J. NOWAK [3], BERIL TALIM [4], NIGEL G. LAING [5], ALAN H. BEGGS [5], HALUK TOPALOGLU [1]

**OP7 DEEP CLINIC AND HISTOPATHOLOGIC PHENOTYPING IN A COHORT OF 17 PATIENTS WITH GYG1-RELATED POLYGLUCOSAN BODY MYOPATHY**
EDOARDO MALFATTI [1], GIANNI MARROSU [2], TANYA STOJKOVIC [1], ANDERS OLDFORS [3], AURELIO HERNANDEZ-LAIN [1], JOHN VISSING [1], PETER VAN DEN BERGH [1], P ASCAL LAFORET [1]

**OP8 DIAGNOSTIC EFFECTIVENESS OF MUSCLE BIOPSY IN NEUROMUSCULAR DISEASES; FOUR YEARS RETROSPECTIVE CRITICAL REVIEW**
BAHATTIN ERDOĞAN [1], SEVGI YIMENICIOĞLU [2], COŞKUN YARAR [3], ERDENER ÖZER [4], KÜRŞAT BORA ÇARMAN [3]

**OP9 RESPIRATORY INVOLVEMENT IN LIMB-GIRDLE MUSCULAR DYSTROPHIES**
LUIGIA PASSAMANO [1], CHIARA DE LUCA [1], VALENTINA CONTESTABILE [1], SONIA AMABILE [1], ANNA ANNUNZIATA [2], GIUSEPPE FIORENTINO [2], LUISA POLITANO [1]

**15:30 - 16:00 Coffee Break**

28 JUNE 2018, THURSDAY

16:00 - 17:00 **SATELLITE SYMPOSIUM – AVEXIS**

17:00 - 18:00 **POSTER PRESENTATIONS**

## POSTER SESSION 1: LIMB-GIRDLE MUSCULAR DYSTROPHIES / PP1 – PP8
**Moderators: Göknur Haliloğlu, Jordi Diaz-Manera**

**PP1 AN EVALUATIONOF CLINICAL AND LABORATORY FINDINGS OF 12 PATIENTS WITH SARCOGLYCANOPATHY**
BAHAR TOKLU BAYSAL [1], FILIZ HAZAN [1], AYŞE GÜLDEN DINIZ [2], GÜLÇIN AKINCI [1], SELVINAZ EDIZER [1], ÜNSAL YILMAZ [1], AYCAN ÜNALP [1]

**PP2 HEART INVOLVEMENT IN LIMB-GIRDLE-MUSCULAR DYSTROPHIES**
ALBERTO PALLADINO [1], ANDREA ANTONIO PAPA [1], MARIANNA SCUTIFERO [1], SALVATORE MORRA [1], GERARDO NIGRO [3], VINCENZO NIGRO [2], CHIARA ORSINI [1], LUISA POLITANO [1]

**PP3 AN OVERVIEW OF PATIENTS DIAGNOSED MUSCULAR DYSTROPHIES WITH MOLECULAR TESTING**
SENEM AYÇA [1], HAMİDE BETÜL GERİK ÇELEBİ [2], HALIL URAL AKSOY [1], SIRRI ÇAM [2], MUZAFFER POLAT [1]

**PP4 LIMB GIRDLE MUSCULAR DISTROPHY TYPE 2A ASSOCIATED WITH HEPATIC INVOLVEMENT: A CASE REPORT**
MERVE FEYZA YÜKSEL [1], ÖZBEN AKINCI GÖKTAŞ [1], ÖMER BEKTAŞ [1], FATMA TUBA EMINOĞLU [2], ZARIFE KULOĞLU [3], SERAP TEBER TIRAŞ [1]

**PP5 CLINICAL POLYMORPHISM OF LIMB-GIRDLE MUSCULAR DYSTOPHY 2A (LGMD2A)**
BAKHYTKUL MYRZALIYEVA [1], MARZHAN LEPESSOVA [2], GAUHAR ABASSOVA [1], ALMA ISSABEKOVA [2]

**PP6 LIMB GIRDLE MUSCULAR DISTROPHY TYPE 2B: A CASE PRESENTED WITH ABDOMINAL AND ANKLE PAIN**
KÜRŞAT BORA ÇARMAN [1], SEVGI YIMENICIOGLU [2], COSKUN YARAR [1]

**PP7 A RARE FORM OF LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD TYPE 2E) IN TRISOMY 21**
DENİZ YÜKSEL [1], ÖZGE DEDEOĞLU [1], FERDA ÖZBAY [2], BERİL TALİM [3]

**PP8 MYOPATHY AND EPILEPSY: A RARE PHENOTYPE IN LIMB-GIRDLE MUSCULAR DYSTROPHY 2L ASSOCIATED WITH ANO5 MUTATION**
EMEL OĞUZ AKARSU , DILCAN KOTAN , MURAT ALEMDAR, ABDULKADIR TUNÇ

28 JUNE 2018, THURSDAY

## POSTER SESSION 2: ALPHADYSTROGLYCANOPATHIES-CONGENITAL MUSCULAR DYSTROPTIES/ PP9 – PP18
**Moderators: Rita Barresi, Bülent Kara**

**PP9 DYSTROGLYCANOPATHIES IN A SINGLE TERTIARY CENTER IN IZMIR**
ULUÇ YIŞ [1], GÖKHAN UYANIK [2], HÜLYA SEVCAN DAIMAGÜLER [4], DEBORAH MORRIS ROSENDAHL [3], AYŞE SEMRA HIZ [1], ERHAN BAYRAM [1], SEBAHATTIN ÇIRAK [4]

**PP10 A CASE OF LIMB GIRDLE MUSCULAR DYSTROPHY 2I DUE TO FKRP MUTATİON PRESENTING AS ACUTE MYOSITIS**
ÖZLEM YAYICI KÖKEN [1], HÜLYA KAYILIOĞLU [1], ÇIĞDEM GENÇ SEL [1], ÜLKÜHAN ÖZTOPRAK [1], BERIL TALIM [2], DENIZ YÜKSEL [1]

**PP11 A NOVEL MUTATION IN FKTN RELATED TO ALFADYSTROGLYCANOPATHY**
ÖZLEM YAYICI KÖKEN [1], ÖZGE TOPTAŞ DEDEOĞLU [1], BERIL TALIM [2], BÜŞRANUR ÇAVDARLI [3], AYŞE AKSOY [1]

**PP12 HOMOZYGOUS POMT1 MUTATION IN A GIRL WITH CONGENITAL MUSCLE DYSTROPHY WITH MENTAL RETARDATION**
DILEK CAVUSOGLU [1], MUHSIN ELMAS [2], BASAK GOGUS [2], BANU DEGIRMENCI [2]

**PP13 A CASE OF MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY TYPE A, 14 WITH COMPOUND HETEROZYGOUS GMPPB MUTATION**
COSKUN YARAR [1], KURSAT BORA CARMAN [1], OZAN KOCAK [2]

**PP14 MEROSIN-DEFICIENT CONGENITAL MUSCULAR DYSTROPHY: A HOMOZYGOUS MUTATION IN THE LAMININ-2 GENE**
PINAR ARICAN [1], NIHAL OLGAC DUNDAR [2], DILEK CAVUSOGLU [3], PINAR GENCPINAR [2]

**PP15 ULLRICH MUSCULAR DYSTROPHY PRESENTING WITH HYPERLAXITY**
SELVINAZ EDIZER , UNSAL YILMAZ , BAHAR TOKLU BAYSAL , AYCAN UNALP

**PP16 COL6A2 RELATED ULLRICH CONGENITAL MUSCULAR DYSTROPHY ASSOCIATED WITH EPILEPTIC ENCEPHALOPATHY**
AYFER SAKARYA GÜNEŞ [1], EMEK UYUR YALÇIN [2], BÜLENT KARA [1]

**PP17 A SPECTRUM OF LAMINOPATHIES: PANDORA'S BOX**
NESIBE GEVHER EROGLU ERTUGRUL [1], GOKNUR HALILOGLU [1], MEHMET ALIKASIFOGLU [2], HALUK TOPALOGLU [1]

**PP18 SEPN1-RELATED CONGENITAL MYOPATHY: A CASE REPORT**
NESLIHAN ÖZCAN , DUYGU GÜNER ÖZCANYÜZ , GÜLEN GÜL MERT, ŞEYDA BEŞEN , MIHRIBAN ÖZLEM HERGÜNER , FARUK INCECIK , ŞAKIR ALTUNBAŞAK , ÖZDEN ÖZGÜR HOROZ , SUZAN ZORLUDEMIR

28 JUNE 2018, THURSDAY

## POSTER SESSION 3: PERIPHERIC NEUROPATHIES AND MYASTHENIA / PP19 – PP27
### Moderators: Müjgan Sönmez, Luis Negrao

**PP19 AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE IN A TURKISH BOY DUE TO A NOVEL HOMOZYGOUS MUTATION IN IGHMBP2 GENE**
ILKNUR EROL [1], OZGUR KUTUK [2], DENIZ YERDELEN [3]

**PP20 NOVEL MUTATION IN PLEKHG5 CAUSES AUTOSOMAL RECESSIVE CHARCOT MARIE TOOTH DISEASE**
ÜLKÜHAN ÖZTOPRAK [1], ÖZLEM YAYICI KÖKEN [1], ÖZGE TOPTAŞ DEDEOĞLU [1], VEHAP TOPÇU [2], ÇAĞRI MESUT TEMUÇIN [3], BERIL TALIM [4], DENIZ YÜKSEL [1]

**PP21 CHARCOT-MARIE-TOOTH DISEASE TYPE 2N: A CASE REPORT**
DUYGU GÜNER ÖZCANYÜZ [1], GÜLEN GÜL MERT [1], NESLIHAN ÖZCAN [1], MIHRIBAN ÖZLEM HERGÜNER [1], FARUK İNCECIK [1], ŞAKIR ALTUNBAŞAK [1], ATIL BIŞGIN [2]

**PP22 HEREDITARY NEUROPATHY WITH GLYPICAN 1 GENE MUTATION**
ISMAIL SOLMAZ , BAHADIR KONUŞKAN , MERT KARAKAYA , HALUK TOPALOĞLU

**PP23 FAZIO LONDE SYNDROME**
MELTEM DIREK , MUSTAFA KÖMÜR , CETIN OKUYAZ

**PP24 NEUROMYOSITIS: A CASE REPORT**
NEBAHAT TAŞDEMIR

**PP25 THREE PATIENTS WITH CONGENITAL MYATENIC SYNDROME**
MAHMUT ASLAN , BİLGE OZGOR , SERDAL OZGOR

**PP26 ANTIBODY LEVELS IN MYASTHENIA GRAVIS PATIENTS**
ANAR TAGIYEV [1], NESIBE EROĞLU [1], ESRA SERDAROĞLU [2], MIRAÇ YILDIRIM [3], DIDEM ARDIÇLI [4], BAHADIR KONUŞKAN [1], BANU ANLAR [1], HALUK TOPALOĞLU [1]

**PP27 OUR EXPERIENCE OF RITUXIMAB IN TWO CASES WITH ANTI-MUSK POSITIVE MYASTHENIA GRAVIS REFRACTOR TO STEROID AND INTRAVENOUS IMMUNGLOBULINE**
AYFER SAKARYA GÜNEŞ , BÜLENT KARA

## POSTER SESSION 4: METHABOLIC DISORDERS / PP28 – PP39
### Moderators: Edoardo Malfatti, Ercan Demir

**PP28 RARE CAUSES OF RHABDOMYOLYSIS: LIPID STORAGE MYOPATHY AND MCARDLE DISEASE**
ABDULKADIR TUNÇ

**PP29 LATE ONSET GLUTARIC ACIDURIA TYPE II: THINK TREATABLE!**
BERRA ÖZBERK[1,2], MERVE SÜLEYMAN[1], NESİBE EROĞLU[1], BERİL TALİM[3], GÖKNUR HALİLOĞLU[1]

**PP30 EXERCISE INDUCED MUSCLE STIFFNES: BRODY MYOPATHY**
CEM PAKETCI [1], HAYRULLAH MANYAS [1], ULUC YIS [1], ERHAN BAYRAM [1], SEMRA HIZ [1], SEBAHATTIN CIRAK [2]

**PP31 LEIGH SYNDROME WITH PTOSIS: A CASE REPORT**
ÖZGE DEDEOĞLU [1], DENIZ YÜKSEL [1], ÇIĞDEM GENÇ SEL [1], ERHAN AKSOY [1], MUSTAFA KILIÇ [2], KADER KARLI OGUZ [3], BERIL TALIM [4]

**PP32 A CASE OF SMALL FIBER NEUROPATHY: FABRY DISEASE**
EMEL OĞUZ AKARSU , MURAT ALEMDAR , DILCAN KOTAN , ABDULKADIR TUNÇ

**PP33 ASSOCIATION BETWEEN MUSCLE CRAMPS, FATIGUE, PAIN AND SERUM 25-(OH) VITAMIN D LEVELS IN MYOTONIC PATIENTS**
NIHAN ERDINC GUNDUZ , AYLIN DIKICI , FILIZ MERYEM SERTPOYRAZ

**PP34 AWARENESS AND KNOWLEDGE LEVEL OF OSTEOPOROSIS IN PATIENTS WITH NEUROMUSCULAR DISEASES- MULTICENTRE STUDY**
BANU DİLEK [1], EBRU ŞAHİN [1], FİLİZ SERTPOYRAZ [2], NİHAN ERDİNÇ GÜNDÜZ [2], AYLİN DİKİCİ [2], ONUR ENGİN [1], ULUÇ YİŞ [5], İHSAN ŞENGÜN [4], ELİF KESKİN PEHLİVAN [3], ELİF AKALIN [1], ÖZLEN PEKER [1]

**PP35 A RARE CAUSE OF NEUROPATHY: ANDERMANN SYNDROME**
HAYRULLAH MANYAS , CEM PAKETCI , DERYA TUNCAY OKUR , ULUC YIS , ERHAN BAYRAM , SEMRA HIZ

**PP36 REVISITING INFANTILE NEUROAXONAL DYSTROPHY (INAD): HIGHLIGHTS!**
ELIF ACAR ARSLAN [1], AHMET CEVDET CEYLAN [2], GÖKNUR HALILOĞLU [3], MERAL TOPÇU [3], HALUK TOPALOĞLU [3]

**PP37 FREQUENCY OF FABRY DISEASE IN PATIENTS WITH CRYPTOGENIC PAINFUL SMALL FIBER NEUROPATHY**
ABDULKADIR TUNÇ , EMEL OĞUZ AKARSU

**PP38 HYPERACUTE MYELOPATHY: A RARE ETIOLOGY AND A GOOD RESPONSE TO AN OUTSTANDING TREATMENT**
NESIBE GEVHER EROGLU ERTUGRUL [1], RAHSAN GOCMEN [2], BANU ANLAR [1], HALUK TOPALOGLU [1]

**PP39 PREDICTORS OF PROGNOSIS AT ADMISSION AND 1ST MONTH IN GUILLAIN BARRE SYNDROME**
ABDULKADIR TUNÇ

## POSTER SESSION 5: DUCHENNE MUSCULAR DYSTROPHY AND INFLAMMATORY MYOPATHIES / PP40 – PP50
**Moderators: Angelini Ferlini, Özlem Hergüner**

**PP40 DUCHENNE MANIFESTING CARRIERS WITH STOP CODON DYSTROPHIN GENE MUTATIONS: TO TREAT, OR NOT TO TREAT, THAT IS THE QUESTION**
PAOLA D AMBROSIO [1], ROBERTA PETILLO [1], VINCENZO NIGRO [2], LUISA POLITANO [1]

**PP41 MUSCULAR DYSTROPHY IN A FEMALE PATIENT WITH A HOMOZYGOUS NONSENSE MUTATION IN DMD GENE: CASE REPORT**
OLCAY ÜNVER [1], GÖZDE YEŞIL [2], GÜLTEN ÖZTÜRK THOMAS [1], GÜNEŞ SAĞER [1], DILŞAD TÜRKDOĞAN [1]

**PP42 TRANSIENT MYOCARDIAL ISCHEMIA FINDINGS IN DUCHENNE MUSCULAR DYSTROPHY; CASE REPORT**
DENIZ ERIS [1], FEYZA AYŞENUR PAÇ [1], SERHAT KOCA [1], AHMET VEDAT KAVURT [1], MERVE MAZE ZABUN [1], HALUK TOPALOĞLU [2]

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**PP43 CHARACTERISTICS OF MOTOR, MENTAL STATUS AND CLINICAL COURSE OF OUR DYSTROPHINOPATHIES**
ÖZLEM YAYICI KÖKEN [1], ÖZGE KUCUR [1], CANDAN TAŞKIRAN [2], ÜLKÜHAN ÖZTOPRAK [1], ÇIĞDEM GENÇ SEL [1], ERHAN AKSOY [1], AYŞE AKSOY [1], TAMER YOLDAŞ [3], DENIZ YÜKSEL [1]

**PP44 META-ANALYSIS OF ATALUREN IN PATIENTS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY**
SUNAY OZDAS [1], CRAIG MCDONALD [2], FRANCESCO MUNTONI [3], EUGENIO MERCURI [4], XIAOHUI LUO [1], GARY L ELFRING [1], HANS KROGER [1], PANAYIOTA TRIFILLIS [1], STUART W PELTZ [1], CRAIG MCDONALD [5]

**PP45 SLOPE ANALYSIS OF 6-MINUTE WALK DISTANCE AS AN ALTERNATIVE METHOD TO DETERMINE TREATMENT EFFECT IN TRIALS IN DUCHENNE MUSCULAR DYSTROPHY**
SUNAY OZDAS , PANAYIOTA TRIFILLIS , MARCIO SOUZA , GARY L ELFRING , HANS KOGER , XIAOHUI LUO , JOSEPH MCINTOSH, STUART W PELTZ

**PP46 LONG-TERM PULMONARY FUNCTION OUTCOMES IN NON-AMBULATORY PATIENTS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY TREATED WITH ATALUREN: 240-WEEK DATA FROM AN OPEN-LABEL EXTENSION STUDY**
SUNAY OZDAS [1], CRAIG M MCDONALD [2], CRAIG CAMPBELL [3], EUGENIO MERCURI [4], FRANCESCO MUNTONI [5], KATHRYN SELBY [6], FENGBIN JIN [1], GIANINA PANAGHIE [1], XIAOHUI LUO [1], JOSEPH MCINTOSH [1], PANAYIOTA TRIFILLIS [1], MARCIO SOUZA [1], STUART W PELTZ [1], MAR TULINIUS [7]

**PP47 A PHASE 2 TRIAL OF THE SAFETY AND PHARMACOKINETICS OF ATALUREN IN PATIENTS AGED ≥ 2 TO < 5 YEARS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY**
SUNAY OZDAS , EDWARD O'MARA , XIAOHUI LUO , PANAYIOTA TRIFILLIS

**PP48 OUTCOME OF CHILDREN WITH JUVENILE DERMATOMYOSITIS: A TERTIARY CENTER EXPERIENCE**
MAHMUT ASLAN [1], SERDAL GUNGOR [1], YILMAZ TABEL [2], BİLGE OZGOR [1]

**PP49 EARLY DIAGNOSIS OF JUVENILE DERMATOMYOSITIS IN A CHILD: THE IMPORTANCE OF MHC-1 OVEREXPRESSION ON SARCOLEMMA**
IBRAHIM ONCEL [1], EMINE SENA ALDEMIR [2], NERMIN UNCU [3], BERIL TALIM [4], UMUT SELDA BAYRAKCI [5]

**PP50 JUVENILE MYOSITIS PRESENTING WITH ANGIOEDEMA**
AYFER SAKARYA GÜNEŞ , BÜŞRA KAYA , ABDULLAH HEYBECI , DERYA SEVEN KAHRAMAN , BURCU HIDIMOĞLU , BÜLENT KARA

## POSTER SESSION 6: MYOPATHIES / PP51 – PP57
**Moderators: Semra Hız, Giacomo Comi**

**PP51 DIAGNOSTIC YIELD OF MUSCLE BIOPSY IN INFANTS: RETROSPECTIVE ANALYSIS OF CLINICAL AND HISTOPATHOLOGICAL FINDINGS**
HÜLYA MARAŞ GENÇ [1], ALEV GÜVEN [1], BERIL TALIM [2]

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**PP52 GENOTYPE-PHENOTYPE CORRELATIONS IN NOVEL FORM OF PYROXD1-RELATED CONGENITAL MYOPATHY**
SERDAL GUNGOR [1], ULUC YİS [2], MAHMUT ASLAN [1], HÜLYA-SEVCAN DAIMAGÜLER [3], KERSTIN BECKER [4], BERIL TALIM [5], GULDEN DINIZ [6], FIGEN BAYDAN [7], SEBAHATTIN CIRAK [3]

**PP53 DISTAL MYOPATHIES: GENOTYPE-PHENOTYPE RELATIONSHIPS OF SIX PATIENTS**
EMEL OĞUZ AKARSU , DILCAN KOTAN , ABDULKADIR TUNÇ , MURAT ALEMDAR

**PP54 TITIN AND TITINOPATHIES: THE STATE OF THE ART**
MARCO SAVARESE , PER HARALD JONSON , ANNA VIHOLA ,JAAKKO SARPARANTA , MRIDUL JOHARI , SALLA VALIPAKKA , PETER HACKMAN , BJARNE UDD

**PP55 FHL1 GENE RELATED X-LINKED REDUCING MYOPATHY TYPE 1A MIMICKING POLYGLUCOSAN MYOPATHY HISTOPATHOLOGY**
AYFER SAKARYA GÜNEŞ [1], HÜLYA MARAŞ GENÇ [2], EMEK UYUR YALÇIN [3], BÜLENT KARA [1]

**PP56 NEUROPATHY? MYOPATHY? NEMALINE MYOPATHY TYPE 2 CASE**
FIGEN BAYDAN , BERK ÖZYILMAZ , FILIZ SERTPOYRAZ , BAKIYE TUNÇAĞ, İREM TIFTIKÇIOĞLU

**PP57 EVALUATION OF THE CHARACTERISTICS OF CRITICAL ILLNESS MYOPATHY PATIENTS**
BEKIR ENES DEMIRYÜREK

## POSTER SESSION 7: GENERAL TOPICS / PP58 – PP67
## Moderators: Giorgio Tasca, Uluç Yiş

**PP58 ANESTHETIC MANAGEMENT OF A CHILD WITH DERMATOMYOSITIS**
EBRU TARIKÇI KILIÇ , HAKAN AKELMA

**PP59 – WITHDRAWED BY AUTHOR**

**PP60 ANAESTHETIC MANAGEMENT IN MUCOPOLYSACCHARIDOSIS**
EREN FATMA AKÇIL

**PP61 EARLY PRESENTATIONS OF SCHWARTZ-JAMPEL SYNDROME: THAT IS ALL IN THE CLINICAL PHENOTYPE!**
IBRAHIM ONCEL [1], GOKNUR HALILOGLU [2], HALUK TOPALOGLU [2]

**PP62 A RARE FAMILIAL TREMOR: HEREDITARY GENIOSPASM**
ESRA SERDAROGLU

**PP63 A RARE CAUSE OF HYPOTONIA; CONGENITAL MYOTONIC DYSTROPHY TYPE 1**
MEHMET FATIH YETKIN [1], MEHMET CANPOLAT [2], MEHMET ALÇI [2], MURAT ERDOĞAN [3], SEFER KUMANDAŞ [2]

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**PP64 CO-EXISTENCE OF POLYNEUROPATHY, OSTEOPOROSIS AND LIMB GIRDLE MUSCULAR DYSTROPHY IN A PATIENT WİTH ANKYLOSING SPONDYLITIS**
FILIZ MERYEM SERTPOYRAZ [1], IREM TIFTIKCIOGLU [2], BAKIYE TUNCAY [3]

**PP65 1P 36 DELETION SYNDROME WITH A POMPE DISEASE-LIKE PRESENTATION**
ELIF ACAR ARSLAN [1], AHMET CEVDET CEYLAN [2], BERIL DILBER [1], EMBIYA DILBER [3], ALI CANSU [1]

**PP66 COHEN SYNDROME: A CASE REPORT**
CEREN GÜNBEY [1], GÜLEN EDA UTINE [2], HALUK TOPALOĞLU [1]

**PP67 NON-TRAUMATIC MYOSITIS OSSIFICANS IN A FOUR-YEAR-OLD GIRL**
OSMAN OĞUZ DEMIR [1], GIZEM KÖKEN [1], NESLIHAN BILGIN [2], HALUK TOPALOĞLU [2]

## POSTER SESSION 8: GENERAL TOPICS / PP68 – PP80
**Moderators: Ayşe Karaduman, Yoram Nevo**

**PP68 ATALUREN AND PHYSIOTHERAPY IN A BOY WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY: 2 YEARS' FOLLOW UP CASE REPORT**
ZİLAN BAZANCİR [1], BİLGE ÖZGÖR [2], MAHMUT ASLAN [2], SERDAL GÜNGÖR [2], BURCU TALU [1]

**PP69 THE ASSOCIATION OF SCOLIOSIS, PAIN, AND RESPIRATORY FUNCTIONS IN DMD PATIENTS**
FILIZ MERYEM SERTPOYRAZ [1], AYLIN DIKICI [2], NIHAN ERDINC GUNDUZ [2], BAKIYE TUNCAY [3]

**PP70 INVESTIGATION OF FACTORS AFFECTING HAND FUNCTIONS IN NONAMBULATORY PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY**
GÜLCAN ALTINOK [1], ÖZNUR YILMAZ [2], AYŞE KARADUMAN [2], İPEK ALEMDAROĞLU GÜRBÜZ [2]

**PP71 INVESTIGATION OF THE RELATIONSHIP BETWEEN GAIT PARAMETERS AND FEAR OF FALLING IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY: A PILOT STUDY**
CANAN İPEK, ÖZNUR YILMAZ, AYŞE KARADUMAN, İPEK ALEMDAROĞLU GÜRBÜZ

**PP72 INVESTIGATION OF HISTORY OF FALLS AND FEAR OF FALLING IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY: A PILOT STUDY**
CANAN İPEK ,ÖZNUR YILMAZ , AYŞE KARADUMAN , İPEK ALEMDAROĞLU GÜRBÜZ

**PP73 INVESTIGATION OF THE RELATIONSHIP BETWEEN ACTIVITY LIMITATION AND UPPER EXTREMITY PERFORMANCE IN NON-AMBULATORY PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY**
GÜLCAN ALTINOK [1], ÖZNUR YILMAZ [2], AYŞE KARADUMAN [2], İPEK ALEMDAROĞLU GÜRBÜZ [2]

**PP74 WHICH ONE HAS THE MOST EFFECT ON PERFORMANCE IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY?: SHORTNESS, FLEXIBILITY AND/OR MUSCLE STRENGTH OF HAMSTRINGS**
LÜTFIYE AKKURT, GÜLLÜ AYDIN, İPEK ALEMDAROĞLU GÜRBÜZ, AYŞE KARADUMAN, ÖZNUR YILMAZ

**PP75 PROFILE OF PATIENTS WITH SPINAL MUSCULAR ATROPHY IN TURKEY: AN ANALYZE FROM KUKAS REGISTRY SYSTEM**
GÜLLÜ AYDIN , NUMAN BULUT , İPEK ALEMDAROĞLU GÜRBÜZ , ÖZNUR TUNCA YILMAZ , AYŞE KARADUMAN

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**PP76 COMPARISON OF THE EFFECT OF AQUATHERAPY AND CYCLE ERGOMETER TRAINING IN A CHILD WITH SPINAL MUSCULAR ATROPHY TYPE II: A CASE REPORT**
NUMAN BULUT , BILGE NUR YARDIMCI , ENDER AYVAT , ORKUN TAHIR ARAN , ÖZNUR YILMAZ , AYŞE KARADUMAN

**PP77 NUSINERSEN AND EARLY PHYSIOTHERAPY IN PATIENTS WITH SPINAL MUSCULAR ATROPHY TYPE 1: CASE SERIES**
ZİLAN BAZANCİR [1], MAHMUT ASLAN [2], BİLGE ÖZGÖR [2], SERDAL GÜNGÖR [2], BURCU TALU [1]

**PP78 CORRELATION BETWEEN FONCTIONAL AMBULATION CLASSIFICATION (FAC) LEVELS AND SERUM VITAMIN B12 LEVELS IN MYOTONIC PATIENTS**
AYLIN DIKICI [1], NIHAN ERDINC GUNDUZ [1], FILIZ MERYEM SERTPOYRAZ [2]

**PP79 COMPLEMENTARY AND ALTERNATIVE THERAPIES IN NEUROMUSCULAR DISEASES**
FILIZ MERYEM SERTPOYRAZ [1], AYLIN DIKICI [2], NIHAN ERDINÇ GÜNDÜZ [2], BANU DILEK [3], EBRU ŞAHIN [3], FIGEN BAYDAN [4], ELIF AKALIN [3], SERAP OZER [5]

**PP80 WHEELCHAIR EVALUATION OF NEUROMUSCULAR DISEASES**
MEHTAP TURANOGLU [1], FILIZ MERYEM SERTPOYRAZ [1], AYLIN DIKICI [2], SERAP OZER [3]

18:00 - 19:00 General Assembly

20:00 - 24:00 **GALA DINNER**

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## 29 JUNE 2018, FRIDAY

**SESSION 3. ADVANCES AND THERAPIES I**
**Moderators: Beril Talim, Antonio Toscano**

09:00 - 09:30 Genetic Diagnosis
**Anna Sarkozy, UK**

09:30 - 10:00 Laminopathies
**Giselle Bonne, FR**

10:00 - 10:30 Dysferlinopathy, Calpainopathy and Imaging
**Giorgio Tasca, IT**

10:30 - 11:00 Contribution of Muscle Biopsy in Diagnosis of LGMD in the Third Millennium
**Rita Baresi, UK**

**11:00 - 11:30 Coffee Break**

**SESSION 4. ADVANCES AND THERAPIES II**
**Moderators: Hayat Erdem, Corrado Angelini**

11:30 - 12:00 Future of Genetics
**Judith Melki, FR**

12:00 - 12:30 Clinical and Molecular Heterogeneity in Limb-Girdle Muscular Dystrophies
**Giacomo Comi, IT**

12:30 - 13:00 Cardiac Involvement in Muscular Dystrophies: Contribution of the Naples's School
**Luisa Politano, IT**

13:00 - 13:30 Treatment of Pompe Disease
**Antonio Toscano, IT**

13:30 - 14:30 **Lunch, SATELLITE SYMPOSIUM - PTC**

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**SESSION 5. ADVANCES AND THERAPIES III**
**Moderators: Duygu Selcen, Judith Melki**

| | |
|---|---|
| 14:30 - 15:00 | Update in Spinal Muscular Atrophy Treatment<br>**Eugenio Mercuri, IT** |
| 15:00 - 15:30 | Therapy of GNE Myopathy<br>**Zohar Argov, IL** |
| 15:30 - 16:00 | Duchenne Muscular Dystrophy: Future Perspectives<br>**Yoram Levo, IL** |
| 16:00 - 16:30 | Sarcoglycanopathies, Therapeutic Approaches<br>**Dorianna Sandona, IT** |
| 16:30 | **Closure of the Meeting** |


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# ABSTRACTS OF INVITED LECTURES

(in alphabetical order of the first Author)

## Metabolic myopathies mimicking LGMD

Angelini C.
*San Camillo Hospital IRCCS, Venice, Italy*

*Objective.* To diagnose metabolic myopathies mimicking LGMD it is useful to perform in hyperckemias or LGMD of unknown cause a dried blood spot (DBS) screening or NGS (next generation screening).

*Method.* Metabolic myopathies are muscle disorders were an enzyme defect may cause a metabolic block with glycogen or lipid accumulation. These muscle disorders might mimic LGMD since they present often a proximal symmetric muscle involvement:adult acid maltase deficiency (AMD) has been named LGMD 2V, now a revised classification has been proposed on the basis of histopathology, MRI changes, clinical criteria and elevated CK. The use of next generation screening (NGS) has allowed to reach a diagnosis as well as organic acid and acyl-carnitine profile tests by GC/MS.

*Results.* AMD pertains to metabolic myopathies and presents a wide spectrum of muscle involvement, spanning severe forms, with infantile onset and cardiomyopathy to relatively benign forms, denominated late-onset Pompe disease (LOPD) where cardiomyopathy is found only in about 10% of cases but respiratory involvement is frequent. AMD is relatively uncommon but important to diagnose disorder, since LOPD patients respond to ERT variably according to age at onset of symptoms in the spectrum from early childhood to late adulthood. The response of muscle weakness is variable among individuals with the classic infantile Pompe where consists in reversal of cardiomyopathy, increased survival, in adult LOPD cases usually 6MWT and GSGC scale are used to monitor outcome. A proximal myopathic presentation can be found also in primary or secondary muscle carnitine deficiency found in riboflavin responsive Lipid Storage Myopathies (RR-MADD) due to ETF-dehydrogenase deficiency.

*Conclusions.* It is important to reach in metabolic cases a definite diagnosis since such myopathies can be treated: AMD responds variably to ERT for 2-4 years and RR-MADD to carnitine/riboflavin supplementation. In undefined LGMD cases a diagnosis can be nowdays reached by NGS.

## GNE myopathy therapy is affected by its pathogenetic enigmas

Argov Z., Mitrani-Rosenbaum S.
*Hadassah, Hebrew University Medical Center*

*Background.* GNE myopathy is caused by gene mutations of the key enzyme in sialic acid (SA) synthesis. Thus, SA supplementation should have theoretically been an efficient metabolic therapy. However, a phase 3 trial of SA slow-release drug has not shown any positive effect (Ultragenyx, Novato, CA).

*Current issues.* 1) Was the trial failure due to pharmacokinetic deficiencies of the drug (not enough SA delivery to muscle)? This may be answered by the ongoing NIH sponsored metabolic treatment trial with ManNac. 2) Are there additional genes (modifiers) involved? This may explain the rare individuals with homozygous GNE mutation who do not develop myopathy and supported by a line of mice homozygous to the same mutation who show no disease at all. 3) Is the disease caused not by a metabolic deficiency but by a lack of normal protein affecting another (yet unidentified) muscle function? The nuclear presence of GNE and its association with myofilaments may indicate this possibility. If so, the planned gene therapy should repair this function. Animal data will be presented. 4) Is impaired autophagy leading to the rimmed vacuoles of GNE myopathy an important downstream defect? Chaperon agents could then be used to overcome such a hypothetical process. Conclusions: clarifying the mechanism of GNE myopathy is an essential factor in planning the next stage of its therapy.

## Contribution of muscle biopsy in diagnosis of LGMD in the third millennium

Barresi R.
*Newcastle upon Tyne Hospitals NHS Foundation Trust, Rare Diseases Advisory Group Service for neuromuscular diseases, muscle immunoanalysis Unit, UK*

Limb-girdle muscular dystrophies (LGMDs) are a large heterogeneous group of inherited diseases that cause progressive muscle weakness and permanent muscle damage. Very few LGMDs show sufficient specific clinical and histological features to allow a potential diagnosis. When the primary genetic modification is unknown, protein analysis is a useful way of directing genetic testing. Immunohistochemistry and Western blot are complementary techniques used to assess the expression of proteins involved in this group of diseases. The muscle biopsy is considered a time and cost-effective test for muscle disorders with ambiguous presentation when there is a limited capacity to

screen for large and numerous genes simultaneously. With the advent of Next Generation Sequencing (NGS), an increasing number of LGMDs can be diagnosed directly by DNA testing. However, many variants identified by NGS are novel and it is important to add experimental data to aid the interpretation. In fact, the effect of novel genetic variants is not always predictable and disruption or preservation of protein expression needs to be confirmed in the muscle. Furthermore, a number of undiagnosed patients may harbour variants in novel genes. In this context, the identification and assessment of specific markers in the muscle biopsy may provide useful information in order to expedite or confirm a diagnosis. In addition, tests on muscle biopsies remain crucial for evaluating the success of applied research and to assess the efficacy of clinical trials.

## Striated muscle laminopathies from gene defects to pathophysiology mechanisms

Bonne G.
*Sorbonne Université-INSERM Center of Research in Myology*

Laminopathies are a diverse and complex group of rare genetic conditions due to mutations in the LMNA gene encoding Lamin A and C, constituents of the nuclear lamina, a meshwork of proteins underneath the nuclear envelope. Striated muscle laminopathies (SML) are the most frequent type of laminopathies (≈ 60% of all laminopathies published cases), that affect skeletal and/or cardiac muscle. SML comprise LMNA related congenital muscular dystrophy (L-CMD), Emery-Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy, type 1B (LGMD1B) and dilated cardiomyopathy with conduction system disease (DCM-CD). Associated with this wide clinical heterogeneity, there is also a large genetic variability as more than 400 different LMNA mutations have been reported so far (www.umd.be/LMNA/, OPALE registry and unpublished data). Over the years, numerous studies have reported that lamin A/C provide structural support to the nucleus, maintenance of nuclear architecture, nuclear migration, and apoptosis, and also take part in chromatin organization and epigenetics, transcription, cell cycle regulation, cell development and differentiation. To study the role of lamin A/C in skeletal and cardiac muscles, and to understand the pathophysiological processes induced by LMNA mutations, we explore both patient biological material and knock-in mouse models that we created, reproducing LMNA mutation identified in SML patients. Using 3D cellular model we set up, we reported defective mechanosensing of human LMNA mutated myoblasts due to abnormal YAP signaling, emphasizing the crucial role of the biophysical attributes of the cellular microenvironment. Exploring KI-Lmna mice, we demonstrated that other signaling pathways, such as MAPK and WNT/β-catenin signaling, contributes to the pathogenesis of the dilated cardiomyopathy of SML. These recent insights of the pathophysiological mechanisms of LMNA mutation will be presented

## Clinical and molecular heterogeneity in limb-girdle muscular dystrophies

Comi G., Magri F.
*Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan - IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

Limb girdle muscular dystrophies are characterized by high molecular heterogeneity, clinical overlap and paucity of specific biomarkers. We recently reviewed a relatively large sample of Italian LGMD (n: 600) which included 366 molecularly defined patients. Their detailed retrospective and prospective data were compared in each LGMD subtype for differential diagnosis purposes. The most frequent forms were LGMD2A (30% of probands) and LGMD2B (22.6%), followed by the sarcoglycanopathies, which together represent the 20.1% of genetically diagnosed patients (21.3%). Within the sarcoglycanopathies, LGMD2D was the most predominant form (46.7%). Thirty-six patients (9.7%) resulted affected by LGMD2I while 14 were diagnosed as LGMD2L (3.8%). Mutations in other LGMD genes were detected only in few patients. Among the autosomal dominant form, the most represented was LGMD1C (67.8% of patients with LGMD1). Age at disease onset, clinical progression, cardiac and respiratory involvement can highly vary between each LGMD. A detailed clinical characterization with muscle tissue analysis remains fundamental in order to guide differential diagnosis and to address molecular tests. NGS is useful to diagnose forms without specific biomarkers. However in this population, several relevant LGMD disease mechanisms remain to be discovered.

## The Jain clinical outcome study in dysferlinopathy

Diaz-Manera J.[1], Fernandez-Torron R.[2], Meredithj J.[3], Mayhew A.[3], Marni J.[4], Mendel J.[5], Straub V.[1]
*[1] Neuromuscular Disorders Unit, Neurology Department, Hospital de la Santa Creu I Sant Pau, BArcelona, Spain; [2] John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne, UK - Biodonostia Health Research Institute, Donostia San Sebastian, Spain; [3] John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne, UK; [4] Centre for Translational Science, Division of Biostatistics and Study Methodology, Children's National Health System, Washington, DC, USA; [5] Nationwide Children's Hospital, Columbus, OH, USA*

Dysferlinopathies present with a variable spectrum of muscle weakness. The Clinical Outcome Study aims to develop understanding of the disease and improve clinical trial readiness.

Participants are assessed on 6 occasions over 3 years (screening, baseline, 6 months, year 1, 2 and 3). 197 subjects were included across 15 sites in 8 countries. At baseline 75% participants were ambulant. Age range is 12-88 years old (mean 40 years). 84% have 2 pathogenic mutations in DYSF.

Physiotherapy assessments include muscle strength (manual muscle testing, MMT; hand held dynamometry, HHD); functional performance using the North Star Assessment for dysferlinopathy (NSAD), Brooke score and Performance of Upper Limb, timed tests (rise from floor, 10 MW, 4 stair climb/descend; Timed Up and Go, 6 MW, and respiratory function testing).

Semi-quantitative MRI analysis was performed on axial T1 weighted sequences collected at baseline visits. This analysis was performed using the Mercuri scale modified by Fisher (0 to 4).

Annual quantitative muscle MRI using Dixon techniques is performed.

Gastrocnemius medialis and soleus were most frequently affected at baseline. A similar pattern of involvement was identified regardless of clinical phenotype.

Significant change is captured from baseline to year 1 in a range of functional outcome measures, strength measurements and quantitative MRI fat fraction. Motor performance assessed by NSAD demonstrated slow but consistent and significant deterioration in scores and confirms NSAD as a dysferlin specific scale.

In conclusion, change in Dysferlinopathy can be measured using physiotherapy outcome measures and quantitative muscle MRI. Results support future study design and help power future clinical trials.

## Future in genetics

Melki J.
*Institut National de la Santé et de la Recherche Medicale (INSERM) UMR-1169 and University Paris sud*

Human genetics started with the map and sequence of the human genome through the Human Genome Project with a great accuracy and established the variations in DNA spelling among humans. The information has been shared making feasible the analysis of all genes in a couple of days. Sharing the numerous variants in genes and their frequency as well as the development of softwares to predict the pathogenicity of variants has been of critical importance for data interpretation. In addition, model organisms have been very useful to establish the link between gene mutation and disease phenotype and to understand gene function. The identification of disease genes allowed numerous applications including i) new diagnostic tools which helps classifying some conditions and end an expensive and potentially invasive diagnostic testing, ii) pharmacogenomics, iii) prognosis especially in cancer, iv) newborn screening for example in phenylketonuria, v) carrier screening especially in communities where severe and untreated disease is particularly common, and vi) gene-based therapy based on gene function, correction of gene mutation or replacing the defective gene or protein.

However, the diagnostic rate remains limited suggesting that a number of factors may affect the efficacy of these strategies: one of them is the acuity of the clinical presentation for variant interpretation and the added value of whole exome sequencing instead of targeted. These technologies have some limitations such as lack of coverage, the difficulty of detecting insertion/deletion (InDel), expanded triplets, mutations in highly homologous genes, or methylation defects. Combining whole exome sequencing with detection of very small InDel in all exons with specific microarrays will be very useful, as well as to test other hypotheses such as oligogenic hypothesis in large cohort of patients or to combine these strategies with transcriptomic/proteomic approaches to identify candidate molecular disease pathway then come back to genomic data.

## Duchenne muscular dystrophy: future perspectives

Nevo Y.
*Tel Aviv University, Schneider Children Medical Center*

Significant progress in diagnosis, establishment of registries, research outcome measures and clinical guidelines have occurred in recent years in Duchenne muscular dystrophy (DMD). In addition increased number of pharma sponsored clinical trials and approval of new treatments by the EMEA (Translarna) and FDA (Eteplirsen) raise hope for further improvement in course, outcome and survival of patients with this disorder. In the current presentation state of the art management of DMD will be presented. Prenatal and neonatal screening in DMD will briefly be discussed. The importance of multidisciplinary surveillance and clinics will be emphasized. Prominent candidate therapeutic agents in pre-clinical stages and various medications already in clinical trials, including new steroids, utrophin up-regulation agents, read-through medications, exon skipping and gene therapy trials will be presented.

## The contribution of the Neapolitan school to the knowledge of heart involvement in muscular dystrophies

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The first description of the myocardial involvement in a patient with Duchenne muscular dystrophy (DMD) was made by a Neapolitan physician, Gaetano Conte, in

1836, 32 years before Duchenne de Boulogne published his report. It seems to be written in the DNA of Neapolitan people the interest for heart problems in muscular dystrophies as in 1976 Giovanni Nigro first described the features of cardiomyopathy in Duchenne patients, at the European Congress of Cardiology. Worthy of mentioning that gene and protein would be discovered 10 years later. He demonstrated that dystrophinopathic cardiomyopathy evolves in a stepwise manner, starting from a pre-symptomatic stage toward an overt dilated cardiomyopathy passing through stages of myocardial hypertrophy, fibrosis and arrhythmias. He also first described as cardiomyopathy may be the only marker of DMD/BMD carriers status in females related to Duchenne and Becker patients. Another of his merits is having understood as other muscular dystrophies such as Myotonic Dystrophy, Emery-Dreyfuss muscular dystrophy and some forms of limb-girdle muscular dystrophy require a continuous cardiological follow-up to avoid the risk of sudden cardiac death.

## Sarcoglycanopathies, therapeutic approaches based on small molecules

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Sarcoglycanopathies are rare autosomal recessive diseases affecting striated muscle, sharing a similar phenotype. The pathology is due to defects in four genes, SGCA, SGCB, SGCD and SGCG coding for $\alpha$-, $\beta$-, $\delta$- and $\gamma$-sarcoglycan (SG), respectively. SGs form a key tetramer that, embedded in the major dystrophin associated protein complex, concurs to the structural stability of the sarcolemma during muscle contraction. When a mutation is present in one of the SG-genes, the entire SG-complex disappears or is strongly reduced and a progressive muscle degeneration leads to the development of the disease. Most of the SG-gene defects are missense mutations leading to the production of folding-defective proteins, recognized and rapidly removed by the quality control system of the cells. At present, no effective treatment is available for sarcoglycanopathy, however, the knowledge of the pathogenic mechanism allowed us to design a novel pharmacological strategy. Indeed, we proved that by using small molecules able to inhibit some components of the degradative pathway, the mutated SG and the SG-complex can be recovered at the plasma membrane. These results have been collected in cell models and in primary myotubes from an $\alpha$-sarcoglycanopathy patient. As a second pharmacological approach, we have also tested compounds known as CFTR-correctors supposed acting on the folding process of SGs. The results obtained are extremely promising, as some of these small molecules are effective in recovering the SG-complex in cell models and in myotubes form both $\alpha$- and $\beta$-sarcoglycanopathy patients. Importantly, although containing a defective member, the rescued SG-complex is functional as the strength of the myotube sarcolemma improved, upon treatment with CFTR-correctors. Our lab is currently focusing on the development and characterization of novel mouse and zebrafish models of the disease, suitable for testing effectiveness of the small molecules in vivo. Experiments aiming at understanding the mechanism of action of CFTR-correctors in sarcoglycanopathies are also ongoing.

## Classification and pathophysiology of LGMD

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Limb-girdle muscular dystrophies (LGMD) are a group of clinically and genetically heterogeneous diseases affecting the skeletal muscle and characterized by a progressive, mainly proximal, muscle weakness. Following the identification of the first LGMD-causative genes, an alphanumerical classification of LGMD subtypes was proposed in 1995. Considering the increasing number of disease genes identified, LGMD nomenclature has become a significant problem. Recently, an ENMC meeting has discussed and approved an update definition of LGMD as well as an improved and more robust LGMD classification system. According to the updated classification, specific conditions are no longer considered LGMDs. LGMD causative genes encode proteins localized within the sarcolemma, cytosol or nucleus of the myocyte. The different LGMD subtypes do not have a unique, common aetiology and this partly justifies the huge clinical heterogeneity observed. With an increasing number of LGMD patients identified, a significant phenotypic overlap between LGMD and other neuromuscular conditions has been observed. Several different pathological mechanisms are involved in the LGMD aetiology, including sarcolemmal instability, enzymatic defects, impaired intracellular trafficking or altered transduction pathways and nuclear functions. The different pathological pathways all lead to a myocyte damage and muscle fiber degeneration. Currently, translational research aims to dissect the pathogenetic causes of LGMD, in order to clarify the natural history for each subtype and develop therapeutic trials for each specific molecular and pathophysiological defect.

## Myofibrillar myopathies

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*Objective.* To review the morphologic, clinical, and genetic spectrum of the myofibrillar myopathies.

*Method.* Clinical, histochemical, immunocytochemical studies, and the mutation analysis.

*Results.* The myofibrillar myopathies are mainly of adult onset with slow progression. However, some patients have infantile and childhood onset with rapidly progressive muscle weakness. The weakness can be proximal or distal or both. Peripheral neuropathy and cardiomyopathy can be associated disorders. The common morphologic features of the disease are hyaline structures, lakes of amorphous material, vacuolar change in the muscle fibers with abnormal, ectopic accumulation of multiple proteins, sometimes with congophilic deposits. The mechanism triggering ectopic protein accumulation is still not fully understood.

*Conclusions.* Myofibrillar myopathies are morphologically distinct but clinically and genetically heterogenous disorders.

## Dysferlinopathy, calpainopathy and imaging

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Muscle imaging through MRI has been implemented in many Neuromuscular Centers as an additional tool in the diagnostic workup of genetic and acquired myopathies. This has led to the definition of imaging patterns of muscle involvement, i.e. a combination of muscles that are selectively affected or relatively spared given a certain genetic defect, in several of the most common limb girdle muscular dystrophies. Calpainopathy (LGMD2A) is one of the muscular dystrophies in which the pattern of involvement on lower limb muscle imaging was first described. Large international collaborative studies are currently ongoing to further clarify the pattern and expand the spectrum of changes in LGMD2A. Another international study has been carried out in a large population of dysferlinopathy (LGMD2B) patients worldwide, confirming the existence of a common distribution of muscle involvement irrespective of the disease phenotypes and providing evidence of a good correlation between extent of MRI changes and clinical severity. The type of involvement in LGMD2A and LGMD2B is partly overlapping with other muscular dystrophies but some clues can help in the differential diagnosis with other LGMDs, such as sarcoglycanopathies (LGMD2C-2F), and with Becker muscular dystrophy. However, the exact contribution of MRI to the diagnostic process of LGMDs still needs to be established. Besides its value as a diagnostic tool, MRI allows a quick global assessment of the patient's "burden of disease" and several recent studies have investigated its usefulness to provide potential measures of outcome, especially using sequences able to sensitively follow intramuscular fat deposition over time.

## Muscular dystrophies with mental retardation

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Mental retardation (MR) in muscular dystrophies is encountered mainly in congenital forms (CMD). Majority of them are related alpha-dystroglycan (a-DG) deficiencies and actually a form of glycosylation problems. Children with merosin deficient CMD usually have normal mentation. MR and features extending into autistic traits is not uncommon in Duchenne muscular dystrophy (DMD). Executive function defects can also be sen in some patients with Becker muscular dystrophy. There is one peculiar form of autosomal recessive limb girdle muscular dystrophy (LGMD2) with MR. This is the LGMD2K (first reported from our centre). These patients invariably present with microcephaly, IQs between 50-60, calf hypertrophy and overall muscle stiffness in about half of the cases. a-DG is substantially reduced from muscle. The mutation is in the POMT1 gene, making this disorder allelic to the Walker-Warbug syndrome. The other clinical entity is choline kinase beta deficiency (Chkb) leading to a form of CMD with severe mental retardation with IQs 35-45 (first reported in our centre with collaboration). There is bizarre mitochondrial changes in muscle, and in some literature this disorder is known as mitochondrial CMD, because the inner lipid layer of mitochondria is involved. There may be ichtyosiform skin changes, heart defects and EEG abnormalities as additional stigmata. LGMD2P is characterised with mild to moderate mental retardation, and is caused by a mutation in the dystroglycan gene (DAG1) primarily. There is only one case reported and that is from our centre. There are other a-DG deficiencies, however not all present with MR. LGMD2T is caused by milder mutations in the GDP-mannose pyrophosphorylase B (GMPPB) gene. There is microcephaly and MR. LGMD2U is caused by particular alleles of the isoprenoid synthase domain containing (ISPD) gene. For the latter two conditions, we need more cases to define a better phenotype.

# ABSTRACTS OF ORAL COMMUNICATIONS

## OP 1

### SMN deficiency causes upregulation of microtubule associated protein 1b (MAP1B) in models of spinal muscular atrophy (SMA)

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*Objective.* Spinal muscular atrophy (SMA) is a devastating neurodegenerative disease which is primarily caused by deletions in the Survival of motor neuron 1 (SMN1) gene. Consequently, functional SMN protein levels are reduced which results in impairments of the cytoskeletal network especially in motor neurons. Disregulations in actin and microtubule binding proteins together with regulatory signalling pathways have been previously described in SMA. Microtubule associated protein 1B (MAP1B) is a crosstalk protein which binds to both microtubules and actin filaments. It is predominantly expressed in nervous system and plays role in regulating microtubule stability. We identified MAP1B upregulation in vitro and in vivo SMA models and focused on consequences of this alteration on microtubule dynamics.

*Method.* Severe SMA Taiwanese mice and SMN knock down motor neuron-like NSC34 cell line were used as in vivo and in vitro SMA model systems to analyze total and phosphorylated MAP1B protein levels. Considering the role of MAP1B on microtubule dynamics, acetylated and detyrosinated alpha tubulin levels together with regulatory tubulin tyrosine ligase enzyme (TTL) were investigated by Western blot.

*Results.* We found a significant upregulation in total and phosphorylated MAP1B protein levels in both, SMN knock down NSC34 cell line and spinal cord tissues of presymptomatic severe SMA Taiwanese mouse. Additionally, we detected a significant upregulation in tubulin tyrosine ligase (TTL) level and a reduction in alpha tubulin detyrosination.

*Conclusions.* Our results suggest that increased level of MAP1B protein in SMN depleted cells cause induction of TTL activity which results in reduced alpha tubulin detyrosination and microtubule stability. Further studies on microtubule stability are ongoing to understand contribution of impaired microtubule dynamics to SMA pathomechanisms.

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## OP 2

### Comparative transcriptome analysis of distinct stromal cell populations during extracellular matrix remodeling in skeletal muscle

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Architectural changes in skeletal muscle regeneration and degeneration are characterized by ECM remodeling involving deposition of extracellular matrix components. These structural changes are primarily a function of various stromal cells and excluding the fiber itself. Several cells were characterized known to involve in remodelling and fibrosis of skeletal muscle under chronic degenerative conditions.

Chronic skeletal muscle degeneration is the end-point of myopathies and dystrophies. Fibrosis is major component of all degenerative conditions and is of outstanding interest since it is progressively and irreversibly limiting kinetic properties, accession of soluble factors that ameliorate regeneration and lastly, a barrier that limits the efficacy of novel therapeutics.

Fibro-adipogenic precursors (FAPs) are in the focus of current research since they are known to contribute to fibrosis in an environment of chronic inflammation. The precise molecular markers of FAPs are obscure and under investigation. Our previous studies revealed the activation of distinct stromal cell sub-populations accompanying different immobilization models regardless of any evidence for inflammation. Thus, we aimed to investigate the transcriptome profile of three distinct stromal populations based on their immunophenotypes in acute injury regeneration model.

Acute injury was induces in 12-week-old male mice via intramuscular cardiotoxin injection and activated stromal cells were harvested using standard protocol at day three. Cells were immunophenotyped and selected based on negativity for CD31, CD45 and CD11b. Within this negative selection, three sub-populations cells were further sorted based on i) Sca1(+)/CD140a(+), ii) Sca1(+)/CD140a(-) and iii) Sca1(-)/CD140a(+). Following RNA extraction and quality control, RNAseq libraries were generated and sequenced on Iontorrent platform. Aligned and analyzed RNAseq data revealed that transcriptomics profile of Sca1(+)/CD140a(-) population exhibited 80% similarity to whole-muscle transcriptome profile of immobilization induced fibrosis and support activation of latent TGF-beta activation. Our results show distinct ECM components to be secreted by diverse subpopulations of skeletal muscle stroma.

## OP 3

### Phosphorodiamidate morpholino oligomers for treatment of Duchenne muscular dystrophy

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*Objective.* Exon skipping is a mutation-specific approach to treating patients with Duchenne muscular dystrophy (DMD). We describe clinical findings with phosphorodiamidate morpholino oligomers (PMOs), which are nucleic acid analogs that selectively redirect pre-mRNA splicing to facilitate dystrophin production.

*Methods.* We describe findings from clinical studies of the PMOs eteplirsen and golodirsen.

*Results.* In clinical studies of exon 51 skipping (eteplirsen; n = 36) and exon 53 skipping (golodirsen; n = 25), internally shortened dystrophin mRNA was observed in all treated patients (per reverse transcription polymerase chain reaction). Eteplirsen increased dystrophin expression 15.5-, 11.6-, and 2.4-fold vs untreated controls (assessed by percent dystrophin-positive fibers, Western blot, and immunohistochemistry intensity, respectively; all, $P \leq 0.007$) in a 180-week study, and 2.8-fold (by Western blot; $P = 0.008$) in a 48-week study. Golodirsen increased dystrophin expression 10.7-fold (assessed by Western blot) over baseline following 48 weeks of treatment. Over 4 years, versus comparable external controls, eteplirsen slowed the ambulatory decline (6-minute walk test difference, 165 m; $P = 0.001$) and the cumulative risk of losing ambulation (83% vs 17%). In 2 clinical studies that included nonambulatory patients, eteplirsen slowed pulmonary decline versus natural history data (assessed by spirometry). *Conclusions.* Eteplirsen and golodirsen demonstrated clinical and biochemical effects in patients with DMD, and ongoing studies of these compounds are further characterizing effects in various patient populations.

## OP 4

### Novel animal models for sarcoglycanopathy

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Sarcoglycanopathies are rare genetic diseases caused by defective sarcoglycans (SG). SGs form a key structural complex contributing to sarcolemma integrity of striated muscles. Most of the reported cases of sarcoglycanopathy are due to missense mutations originating a full length but folding-defective protein that is prematurely degraded, thus leading to the strong reduction of the SG-complex on the sarcolemma. We already published exciting results about a novel therapeutic approach based on small-molecules helping protein folding and leading to proper SG-complex localization on sarcolemma of primary myotubes from sarcoglycanopathy patients. However, to confirm in vivo this strategy, we need animal models expressing folding-defective sarcoglycans. To accomplish this task we adopted two independent, but complementary, strategies based on zebrafish and mouse models. We first decided to apply the CRISPR/Cas9 technique for the generation of both KO- and KI-SG in zebrafish. We already obtained delta-SG and beta-SG KO lines, whose characterization is ongoing and that we will use for the transient expression of WT or mutated human SGs. Presently, we are also setting up different approaches for the effective generation of the KI models. Concomitantly, considering the large number of reported sarcoglycan missense mutants, we decided to take advantage of the null background of the alpha-SG-KO mouse to transduce, by recombinant Adeno Associated Virus, different missense mutants of the human alpha-SG. The early injection of the virus in the legs of 2-day old pups led to the development of a dystrophic phenotype in the presence of the mutated protein, whereas the WT protein induced the rescue of the phenotype. The setup of a quantitative method is now ongoing. We are confident that the combined use of both zebrafish, suitable for fast drug screening, and mouse, the preferred model for preclinical studies, will help us in the identification of an effective therapy for sarcoglycanopathy.

## OP 5

### Targeted sequencing with expanded gene profile enables high diagnostic yield in non-5q-spinal muscular atrophies

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Spinal muscular atrophies (SMA) is a heterogeneous group of disorders characterized by muscular atrophy, weakness, and hypotonia due to suspected lower motor neuron (LMN) degeneration. In a large cohort of 3465 individuals suspected with SMA submitted for SMN1 genetic testing to our routine diagnostic laboratory, 48% carried a homozygous SMN1 deletion, 2.8% a subtle mutation and an SMN1deletion while 49.2% remained undiagnosed. Recently, several other genes implicated in SMA/LMND have been reported. Despite several efforts to establish a diagnostic algorithm for non-5q-SMA, data from large-scale studies are not available. We tested the clinical utility of targeted sequencing in non-5q-SMA by developing two different gene panels. We first analysed 30 individuals with a small panel including 62 genes associated with LMND using IonTorrent-AmpliSeq target enrichment. Then, additional 65 individuals were tested with a broader gene panel encompassing up to 479 genes implicated in neuromuscular diseases (NMD) with Agilent-SureSelect target enrichment. The NMD panel provided a higher diagnostic yield (45%) than the restricted LMND panel (13%). Non-diagnosed cases were further subjected to exome or genome sequencing which solved 9.4%. In conclusion, individuals with non-5q-SMA are efficiently diagnosed by using large gene panels covering a broad NMD spectrum.

## OP 6

### A cohort of congenital myopathy patients from a tertiary neuromuscular referral center: diagnostic yield from next generation sequencing (NGS) techniques

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*Objective.* To evaluate clinical and histopathological features of patients with congenital myopathies (CM) from a referral center, and to describe utility of NGS-based diagnostic tools.

*Methods.* 68 patients (from 61 families) with a diagnosis of CM were included. A NGS-based neuromuscular disease (NMD) gene panel including > 450 neuromuscular disease genes, and/or whole exome sequencing (WES) was performed. *Results.* The mean age of the patients was 8.5 years, and male/female ratio was 38/30. There were 7 affected siblings, with consanguinity in 36 families. Based on the index cases, the mean age of symptom onset was 13 months (birth-9 years). Presentation was in the newborn period (42%), < 2 years (44%), and ≥ 2 years of age (14%); with facial (56%) and cervical weakness (50%), joint contractures (24%), and ophthalmoparesis (12%). Respiratory problems and scoliosis were present in 30% and 27% of patients, respectively. Muscle biopsy was performed in 50 index cases and 3 affected siblings, and revealed distinctive myopathic features [(nemaline rods (n = 11), cores (n = 7), centronuclear myopathy (n = 2), fibre-type disproportion (n = 2)] in 42%, and non-specific myopathic changes in 58%. Pathogenic mutations were detected in 21/61 (34%) of the families by using the gene panel (n = 11) and/or WES (n = 10). Variants of unknown significance (VUS) were identified in 10/61 (16%) families by the gene panel (n = 7) and/or WES (n = 3). Mutations in RYR1 (n = 5) were the most prevalent disease cause, followed by TTN (n = 4) and NEB (n = 3).

*Conclusions.* A definitive or probable molecular genetic diagnosis was made in 50% of families by using the NMD-gene panel (58%, 18/31) and/or WES (42%, 13/31). NGS-based tools (gene panel or WES) improved diagnosis with heterogeneous phenotypic and histopathologic presentations, especially related to large genes like RYR1, TTN and NEB, while creating an extra challenge posed by detection of an increasingly large number of VUS, as presented in this cohort.

## OP 7

### Deep clinic and histopathologic phenotyping in a cohort of 17 patients with GYG1-related polyglucosan body myopathy

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*Objective.* Detail the clinical and morphological features in patients with polyglucosan body myopathy 2 associated with GYG1 gene mutations. Methods: We retrospectively analysed muscle symptoms and muscle biopsies from 17 patients from 12 families with pathogenic GYG1 gene mutations.

*Results.* Seven patients were male and ten patients were female. Age at onset varied from 15 to 79 years. Initial symptom was lower limb girdle weakness (4 patients), distal lower limb weakness (3 patients), upper limb girdle weakness (2 patients), muscle fatigability at running (2 patients), scapulo-peroneal weakness (1 patient), asymmetric hand and lower proximal limb weakness (1 patient), exercise intolerance with myalgia followed by limb girdle weakness (1 patient), and sports difficulties (1 patient). Clinical course was slowly progressive, with extension of weakness to proximal segments in distal patients. Associated mild axial weakness was found in 3 patients. Only 1 patient developed facial weakness. Strikingly asymmetric weakness was noted in 6 patients. Proximal patients developed marked waddling gait necessitating the use of a cane/rollator, or intermittent wheelchair. Distal patients developed stepping gait. Serum CK were normal or slightly elevated in 8 patients, and highly elevated in 9 patients. None of the patients developed primary cardiac or respiratory involvement. Muscle biopsy showed vacuoles filled with hyperintense PAS-positive material partially resistant to $\alpha$-amylase in 5-50% of fibers (14 patients). All patients presented one homozygous or two compound heterozygous GYG1 mutations. Nine patients were homozygous for the common c.143 + 3G > C mutation and three were heterozygous. Conclusion: Polyglucosan body myopathy 2 shows an extremely variable clinical phenotype including slowly progressive limb girdle, scapulo-peroneal or distal, often-asymmetric weakness. Muscle fatigability, effort intolerance and myalgia are rare manifesting symptoms. On the other hand, the histopathologic phenotype is homogenous and easily recognisable. A multicentre international natural history study will be useful in view of a possible therapeutic approach.

## OP 8

### Diagnostic effectiveness of muscle biopsy in neuromuscular diseases. Four years retrospective critical review

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Most of the neuromuscular diseases are genetic and progressive. It is important to make a timely and correct di-

agnosis for treatment guide, follow-up of the progression and genetic counseling to be given to the family. The aim of this study is to analyze the histopathological evaluation process and results of muscle biopsies and to evaluate the contribution to the diagnosis and management decisions of the disease.

*Method.* Muscle biopsy evaluation has been started on January 2013 in Anatomic Pathology Laboratories at Eskişehir Community Hospital. Support had been taken from Izmır 9 Eylül University Pathology Department for two years in order to get technical standards and academic experience. A retrospective study was carried out in 160 muscle biopsies evaluated between 2013 and 2017 in the laboratory. Electronic hospital records and pathology reports were reviewed all together for preanalytic and analytic process data; gender, age, symptoms, signs, age of beginning of the symptoms, duration between the symptoms and muscle biopsy, family history, creatinine kinase level (CK), electromyography (EMG), prediagnosis, specimen adequacy, histopathologic diagnosis.

*Results.* 53,8% (n = 86) of the muscle biopsy specimen belong to children (C) and 46,3% (n = 74) belong to adults (A); 40% female (F), 60% male (M) predominates this ratio is (F: 29,1%, M: 70,9%) in the children and (F: 52,7%, M: 47,3%) in the adults. Muscle weakness was most common associated symptom in 42,6% (n = 66), hypothonic infant in 15,5% (n = 24), fatigue in 12,9% (n = 20) and coincident high CK levels in 11,6% (n = 18). Duration between beginning of the symptoms and muscle biopsy was between one month and 360 months, with the mean 57 months (Children (C) 23 months, Adults (A) 98 months). EMG before biopsy was reported in 50,6% (n = 81) (C 22,1%, A: 83,8%). Myopathic changes were found in 52 (32,5%) of these cases. 71,2% (n = 114) of cases had CK levels of them 27,5% (n = 44) were normal levels, 15,6% (n = 25) were slightly elevated, 28,1% (n = 45) were high. Consanguinity or suspected family history of muscle disease incidence was 33,1% (n = 53). Of the patients 33,1% (n = 53) had negative family history. Muscle weakness was reported most common with a rate of 42,6% (n = 66), hypotonic infant 15,5% (n = 24), fatigue was 12,9% (n = 20). Clinical preliminary diagnosis before muscle biopsy was myopathy/dystrophy in 60,1% (n = 96) [myopathy in 41,9% (n = 67), myopathy/dystrophy in 14,4% (n = 23), dystrophy in 3,8% (n = 6)], patients searched for high CK levels in 11,3% (n = 18), metabolic/mitochondrial disease in 10% (n = 16), hypothonic infant (myopathy ?) in 6,9% (n = 11), inflammatory myopathy in 7,5% (n = 12). Routine histochemical evaluation revealed myopathic/dystrophıc diagnosis in 71,2% (n = 114). 57% (n = 65) of these (40,6% of all patiens) were specified more with enzyme histochemical and immune histochemical methods. Neuropathic change has been observed in 9,4% of the cases. Nonspecific muscle biopsy results were 8,8% (n = 14), normal histology results were 10,6% (n = 17). Secondary diagnosis with additional tests revealed dystrophinopathy in 11,3% (n = 18), metabolic/mitochondrial diseases in 9,4% (n = 15), dysferlinopathy in 6,2% (n = 10), inflammatory myopathy in 5% (n = 8) (DM: 1, PM: 4, IBM: 3), lipid storage disease in 1,9% (n = 3), glycogen storage disease in 2,5% (n = 4), sarcoglycanopathy in 1,3% (n = 2), alpha distroglycanopathy in 1,3% (n = 2), myotonıc dystrophy in 0,6% (n = 1), central core disease in 0,6% (n = 1).

*Discussion.* The first step in the clinical approach is to obtain adequate and accurate information on disease symptoms. Signs and symptoms were provided in 96,9% (n:155) of patients. Muscle weakness was the most common sign with 42,6% (n = 66) in our study. If weakness distribution is at proximal part of legs and arms myopathy is the most probable diagnosis; If the neurology examination is normal general weakness and fatigue does not correlate myopathy but the duration of the exercise that elaborates fatigue and weakness is important. Hypotonıc infant is a feature of some muscular disease like spinal muscular atrophy (SMA), congenital muscular dystrophy (CMD), congenital myopathy. Muscle biopsy evaluation is essential for neuromuscular hypotonia. In our study hypotonıa was most common symptom at pediatric population in 27,9% (n = 24), it was 15,5% in all cases. Age onset of the symptoms, duration, course are important to determine. Myopathy may cause constant weakness (inflammatory myopathy, muscle dystrophy) or episodic weakness (glycolytic pathway disturbances, periodic paralysis). Episodic disorders are characterized with acute weakness resolving within hours or days. Most of the myopathy are transmitted genetically the family history takes importance. Family tree must be described for autosomal dominant, recessive, X-linked inheritance. Electromyography (EMG) is use full for differential diagnosis between denervation myopathy, myotonia, muscle-nerve junction disease. Electromyography is also hard to perform for myopathic process at pediatric population, sufficient contraction may not be obtained, at young age groups ıt may not give precise results. Muscular dystrophy (Dystrophinopaty, sarcoglycanopathy, merosinopathy…), congenital myopathy, myositis (Dermatomyosistis, polymyositis, inclusion body myositis), vasculitis, especially meatbolic myopathies (type 2 glycogenosis, phosphorylase defficiency, phosphofructokinase defficiency, lysosomal storage disease, lipid myopathies, mitochondrial myopathies) are the primary disease that require muscle biopsy In our study it is remarkable that there were 6 patients also genetically diagnosed as glycogen storage disease and lipid storage disease. Five of them had admitted with refractory polymyositis, one was exploring for CK height. Pathologic diagnosis is indispensable when progression of treatment is considered. Duration between muscle biopsy and onset of the symptoms is one of the most important indicator in the study. This interval was 23 months in pediatric patients, 98 months in adult patients. This long interval reflects difficulty of the diagnosis. Conclusion The disadvantage of our study is that due to the limitation of immunohistochemistry panel, necessary additional tests could not be done in some patients and results could not be supported with Western Bloot, Electron microscopy. less number of confirmatory molecular genetic support is a major drawback. Muscle biopsy is indispensable to establish an etiologic diagnosis and is a component of the identification of prognostic prediction and therapeutic planning as well as diagnostic data. Only 21 patient had both pathological and genetic diagnosis confirmed. Genetic diagnosis did not confirm the pathologic daignosis at one patient who had mitochondrial myopathy at the muscle biopsy. We believe that improving the technical infrastructure, eliminating immunohistochemical panel deficiencies, adding Western Bloot studies, and providing EM and molecular genetic research support, produce more productive results.

## OP 9

### Respiratory involvement in LIMB-girdle muscular dystrophies

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LGMD is a highly heterogeneous group of very rare neuromuscular disorders characterized by autosomal inheritance. To date, over 30 distinct forms of LGMD have been identified, with both autosomal dominant (LGMD1A-1G) and recessive (LGMD2A-2W) inheritance. Restrictive respiratory syndrome is a common clinical manifestation of muscular dystrophies, but the incidence of respiratory involvement may vary with th different types. As prognosis of muscular dystrophy patients may be directly related to cardiac and respiratory status, surveillance and timely management of cardiac and respiratory complications are important. We present the prevalence of respiratory insufficiency in a group of 258 LGMD patients molecularly defined, and followed for many years at the Cardiomyology and Medical Genetics of University of Campania. Calpainopathy was the more frequent diagnosis (28%) followed by sarcoglycanopathies (22,4%) and dysferlinopathy. Patients with mutations in FKRP and ANO5 accounted for a further 8,9% of cases. A restrictive syndrome was prevalent in patients affected by LGMD2C-2F, 2I and 2N subtypes, and with a less frequency in those affected by LGMD2A and 2B. The respiratory involvement was rare in the remaining forms. In some cases the involvement was very severe and required mechanical support (LGMD2C-2F and 2I). No correlation was found with the severity of heart involvement.

# ABSTRACTS OF POSTER COMMUNICATIONS

(listed in order of presentation)

## Session 1. Limb-girdle muscolar dystrophies

### An evaluationof clinical and laboratory findings of 12 patients with sarcoglycanopathy

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*Objective.* Limb girdle muscular dystrophies (LGMDs) are characterized by high molecular heterogeneity, clinical overlap and a paucity of specific biomarkers. Their molecular definition is fundamental for prognostic and therapeutic purposes. The aim of the study was to analyze the clinical and laboratory characteristics of children with sarcoglycanopathies.

*Method.* The study was carried out retrospectively in the Pediatric Neurology Department of our hospital between 2007 and 2017. Patients with LGMD were evaluated regarding the clinical and laboratory findings including creatine kinase, electrophysiology, muscle biopsy with immunocytochemistry and molecular genetics.

*Results.* The mean age at onset was 6,4 years (range 1,5-9 years). In our series the mean age for the LGMD phenotype was much lower than literature findings. Four patients (%33) had just proximal presentation of weakness, 73 (25%) had symptoms of just distal weakness and 4 (33%) patients had more prominent distal weakness but were proximally weak as well. Six patients (50%) had no initial complaints, but creatine kinase was elevated. Three patients (50%) had calf hypertrophy, 2 (12%) had scapular tears, and 5 patients (41%) had a DMD phenotype. The phenotype was mild and ambulation was maintained in all patients. Six 50(%) patients had gamma, 4 (33%) patients had alpha + gamma, 1 (8,3%) patient had beta SGC staining defect and 1 (8,3%) patient had diffuse myotilin expression in muscle biopsy. Six (50%) patient was LGMD type 2C, 4 (33%) patient was type 2D, 1(8,3%) patient was type 2E and 1(8,3%) patient was type 1A.

*Conclusions.* LGMD types 2C and 2D was the most frequent forms in our series. LGMD diagnosis was made by careful examination, muscle biyopsy immunohistochemistry followed by genetic analysis. Genetic counseling, antenatal diagnosis and preventive measures are expected to be at the forefront in the coming years with the widespread use of genetic tests for early diagnosis.

### Heart involvement in limb-girdle muscular dystrophies

Palladino A.[1], Papa A.A.[1 2], Scutifero M.[1], Orsini C.[1], Petillo R.[1], Morra S.[1], Nigro G.[2], Politano L.[1]

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LGMD is a highly heterogeneous group of very rare neuromuscular disorders whose common factor is their autosomal inheritance. To date, over 30 distinct subtypes of LGMD have been identified, inherited in both autosomal dominant (LGMD1A-1G) and recessive (LGMD2A-2W) fashion. Cardiac disease is a common clinical manifestation of muscular dystrophies. Cardiomyocites as well as specialized conducting myocardial fibres may be affected by the dystrophic process. The incidence and nature of cardiac involvement vary with different types of muscular dystrophies. As prognosis of muscular dystrophy patients may be directly related to cardiac status, surveillance and timely management of cardiac complications are important. We present the prevalence of cardiac disease in a group of 258 LGMD patients molecularly defined, and followed for many years at the Cardiomyology and Medical Genetics of University of Campania. Calpainopathy was the more frequent diagnosis (28%) followed by sarcoglycanopathies (22,4%) and dysferlinopathy. FKRP and ANO5 mutations accounted for a further 8,9%. Myocardial disease, resulting in dilated cardiomyopathy and heart failure was found mainly in patients affected by LGMD2C, 2F, 2I, 2J, 2K, 2M and 2N subtypes, while anomalies of the conduction system leading to arrhythmias often requiring pacemaker or defibrillator implantation were more frequently observed in patients with LGMD1B, 1E or LGMD2R subtypes. We will provide an efficient strategy for the expertise and management of these diseases.

### An overview of patients diagnosed muscular dystrophies with molecular testing

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*Introduction.* The muscular dystrophies are a subgroup of the primary myopathies with genetic etiology, which characteristically have "dystrophic" features on muscle biopsy and progressive muscle weakness. We present patients who referred to our clinic and diagnosed muscular dystrophies with moleculer testing.

*Case reports.* We present two siblings with age of 4 and 2 years with elevated serum CK levels, muscle weakness and contractures of the lower limbs. Both of the siblings had proximal muscle weakness power of grade 3/5. They had contractures on their lower limbs. Muscle biopsy showed dystrophic pattern and a completely negative reaction for merosin. The magnetic resonance imaging (MRI) revealed diffuse white matter hyperintencity supporting the diagnose and we suspected the diagnose of merosin deficient muscular dystrophy (MDC1A). Sequencing of two siblings revealed a novel homozygous frameshift mutation p.N55Mfs*16(c.163_163delA) within the LAMA2 gene. This mutation is leading to a premature stop codon and no reported in the literatüre. Second case is 17-year-old female and she had suffered from muscle weakness. Deep-tendon reflexes were negative. She had positive Gower's sign and proximal muscle weakness. She had foot-drop and atrophy of lower extremities. Her feet showed a mild pescavus deformity. She had first degree of atrioventriculer block. Muscular histology was compatible with muscular dystrophy. LMNA gene sequence analysis including all coding exons and exon-intron boundiries was

done and LMNA NM_170707.3:c.734T > C; (p.Leu245Pro) heterozygous missense mutation was detected. This mutation was first reported by from Turkish population. Her parents were no carriers of the mutation. Third case is 13 years old girl had suffered from proximal muscle weakness for a few months. Muscle biopsy showed focal deficiency of sarkolemmal beta sarkoglican expression. Histopathological findings confirmed LGMD type 2E disease. SGCB gene sequence analysis detected heterozygous p.A9A(c.27A > C) NM_000232.4 mutation due to LDMD 2E.

*Discussion*. Consanguineous marriage is frequently seen in Turkey. The moleculer diagnosis is essential for genetic councelling and prenatal diagnosis when required.

## Limb-girdle muscular distrophy type 2A associated with hepatic involvement: a case report

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*Purpose.* Limb-girdle muscular dystrophy (LGMD2A) type 2A (is an autosomal recessive limb-girdle muscular dystrophy characterized by progressive, symmetrical weakness of the proximal limb and girdle muscles without heart involvement or intellectual disability). Hepatic involvement is not typical for LGMD2A. We want to present a case admitted with liver failure and elevated blood creatine kinase (CK) levels and was diagnosed with LGMD2A.

*Case.* A 6-year-old male was referred by the Department of Pediatric Metabolism due to elevated serum CK levels. When he was 8 months old, he admitted to hospital with fever and vomiting; liver function tests (AST-ALT) and blood CK levels were elevated. Hepatic fibrosis was detected in abdomen ultrasonography. The tests for liver failure etiology and metabolic diseases were resulted in normal ranges. He had hepatocellular reactive changes in liver biopsy; and the muscle biopsy was nonspesific. His parents are cousins and his uncle had died when he was 15 years old because of esophageal variceal hemorrhage due to liver failure. Neuromotor development stages of our patient progressed appropriate for his age. In neurological examination, it was determined that he had atrophy in upper extremity proximal muscles, pseudohypertrophy in lower extremity calf muscle and wing scapula. The muscle tonus and muscle strength were normal, the Gowers was negative. The MLPA analysis for Duchene Muscular Dystrophy resulted as normal. The liver biopsy was repeated for the second time; however, no etiology could be determined. The whole exom sequence was consistent with LGMD2A.

*Conclusions.* Hepatic involvement is not typical for this disease, and hepatic failure associated LGMD2A has not been reported in the literature.

## Clinical polymorphism of limb-girdle muscular dystophy 2A (LGMD2A)

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*Purpose.* To show clinical polymorphism of LGMD2A based on the description of two cases in one family.

*Material and methods.* Two brothers aged 9 and 19 years with neuromuscular pathology symptoms. Clinical, EMG and genetic studies were conducted.

*Results.* Nationality: Kazakh. Marriage of parents is closely related.

*Case 1.* 9 years old boy. Debut of complaints at the age of 6 years in the form of frequent falls, walking on the toes, difficulty in getting up, climbing stairs, running. Gait impairment, arm weakness developed over time. Neurological status: Walking on the distal foot. Muscle weakness in the proximal arms, legs, axial musculature. Muscular hypotension. Biceps and knee reflexes are absent, Achilles are depressed. Moderate hypotrophy of the shoulder and pelvic girdle muscles. Winged scapula. Lumbar hyperlordosis. Pseudohypertrophy of the leg and femur muscles. Equinovarus feet. CK-5129, EMG-primary-muscular type lesion.

*Case 2.* 19 years old young man. Debut of complaints at the age of 17 years: muscle weakness in the hands and legs, difficult walking, weight lifting. Weakness in the legs, a significant weight loss developed over time. Neurological status: Muscle weakness in the proximal arms, legs. Pronounced hypotrophy of the shoulder girdle muscles, distal section of upper and lower extremities. Biceps and knee reflexes are absent, Achilles are preserved. Winged scapula. Moderate lumbar hyperlordosis. Pseudohypertrophy of deltoid, gastrocnemius muscles. CK-1730. EMG-primary-muscular type lesion. DNA sequencing: a homozygous mutation was found in the 21 exon of the CAPN3 gene (chr15:42702843C > T, rs768090444), which led to a stop codon (p.Arg748Ter, NM_000070.2)

*Conclusions.* The presented clinical cases of LGMD2A in one family show clinical polymorphism of the disease: different age of debut, course and progression of the disease. A previously unknown homozygous mutation was found. The mutation frequency in the control ExAC sample is 0.0008%.

## Limb-girdle muscular distrophy type 2B: a case presented with abdominal and ankle pain

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*Objective.* Limb girdle muscular dystrophy type 2B is a rare subtype of muscular dystrophy, the predominant feature of which is muscle weakness. The disease is caused by an autosomal recessively inherited reduction/absence of muscle dysferlin due to a mutation in dysferlin gene at 2p12-14. We report a 15 year girl who presented with severe transient abdominal and ankle pain.

*Case report.* She has been suffering for one year and had pain 2-3 times a week especially in the morning and continue for 20 minutes then relief after vomiting. The laboratory investigations revealed CK level as 5858 U/L. Her detailed medical history cleared that she has mild difficulty in walking and climbing. Muscle biopsy showed markedly pathologic changes in shape and size of fibres. Necrotic, basophilic and split fibers seen with increased nuclear internalization (approximately 10%). No collagen deposition or vacuoles seen. Immunostaining for dysferlin was extendedly low and absent in some fibers. The genetic analysis revealed DYSF gene mutation on 2p12-14.

*Conclusions.* Our case describes an atypical presentation of limb-girdle muscular distrophy type 2B, the predominant feature of which is abdominal pain.

### A rare form of limb-girdle muscular dystrophy (LGMD type 2E) in trisomy 21

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*Objective.* Down syndrome is the most common chromosomal disorder and muscle hypotonia is seen nearly all of them. We present a previously unreported case with down syndrome and sarcoglycopathia.

*Case.* A 4-year-old down syndrome boy suffered from progressive muscle weakness was consulted to pediatric neurology. He could sit along but not walk and deep tendon reflexes were hipoactive. Lacking of abilities in motor and language areas are detected in neurodevelopmental tests. No cardiac abnormalities were reported. Serum creatine kinase (CK) levels were elevated to 100 times of normal values. In immunohistochemical studies in muscle biopsy; the complete absence of all four sarcoglycans was indicated. Mutation analysis revealed a novel homozygous mutation at c.703_704insA in SGCB gene. This result presents a novel underlying genetic mechanism for LGMD type 2E and segregation analysis showed that both parents are heterozygous for the identified mutation.

*Conclusions.* Although hypotonia in Down syndromes may be due to the natural history of the disease, it is necessary to keep in mind that measurement of serum CK value at least once likely to be a possible muscle disease.

### Myopathy and epilepsy: a rare phenotype in limb-girdle muscular dystrophy 2l associated with ano5 mutation

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*Introduction.* Limb-girdle muscular dystrophy (LGMD) caused by mutations in anoctamin 5 (ANO5) gene was reported to be the third common form. It is mainly reported from Northern and Central Europe. Here we report the case of a Turkish male patient with a mutation of ANO5 gene.

*Case.* A 55-year old male from a Turkish family was admitted to our neuromuscular clinic with progressive muscle weakness and seizures. The first symptom was started at twenties with difficulty in running, climbing stairs and rising from the floor. But he first admitted to the hospital when he started to have seizures at 36 years of age. His seizures were characterized by generalized tonic clonic seizures and he was first treated with phenytoin. However, seizures were poorly controlled and phenytoin treatment was switched with levetiracetam which significantly reduced the frequency of seizures. He referred to our center at age of 50 when he noted weakness in upper limbs and had trouble in walking. On physical examination calf hypertrophy was noted bilaterally. Neurological examination revealed proximal lower extremity weakness predominantly in extensor muscle groups with medical research council scale (MRC) 2/5, and distal upper limb predominantly in wrist extensors with MRC 2/5. CK level was 1.050 IU/l. Leg muscle MRI showed atrophy of the thigh muscles. Electromyography showed an electrophysiological myopathy with short duration motor unit potentials diffusely. Muscle biyopsy showed fiber size variation, internal nuclei and occasional split fibers. Immunohistochemical analysis showed normal dysferlin staining. Molecular genetic investigations showed homozygous mutation in c.2141C > G in exon 5.

*Discussion.* We present the first patient with ANO5 mutation associated with epilepsy and myopathy up to date. We emphasize that this rare and peculiar clinical picture expands the phenotypic spectrum associated with ANO5 gene mutations.

## Session 2. Alphadystroglycanopathies-congenital muscular dystropties

### Dystroglycanopathies in a single tertiary center in Izmir

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*Aim.* Dystroglycanopathies are a subgroup of congenital muscular dystrophies and they are a highly heterogeneous disorders, clinically characterized by muscle weakness and variable involvement of eyes and central nervous system. We provide a study of patients with dystroglycanopathies in a tertiary center in Izmir-Turkey.

*Methods.* Clinical and genetic findings of patients with dystroglycanopathies followed in Dokuz Eylül University, School of Medicine were evaluated. The spectrum of clinical severity for dystroglycanopathy patients was described using the classification proposed by Cirak et al.

*Results.* Twenty-four patients were evaluated. Fifteen of the patients were in the MEB/FCMD group followed by Walker-Warburg syndrome like (n = 4), congenital muscular dystrophy with mental retardation (n = 4) and congenital muscular dystrophy with cerebellar involvement (n = 1). Twenty-one patients had genetic diagnosis. POMGNT1 was the most mutated gene. Most of the patients with POMGNT1 had c.1814G > A mutation (p.R605H). All patients except congenital muscular dystrophy with mental retardation had varying degrees of structural eye and central nervous system abnormalities.

*Conclusions.* Muscle eye brain disease was the most common subtype in dystroglycanopathies followed in our tertiary center. c.1814G > A mutation (p.R605H) in exon 21 of the POMGNT1 gene is an apparently common founder mutation in the Turkish population.

### A case of limb-girdle muscular dystrophy 2l due to FKRP mutation presenting as acute myositis

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Our aim is to report a case presenting as acute myositis who was diagnosed as limb girdle muscular dystrophy 2I (LGMD2I) due to FKRP mutation. A 6-year-old girl of consanguineous parents was referred our clinic with acute weakness of proximal

muscles after an acute upper respiratory tract infection. Physical examination showed hip and proximal limb weakness in addition to global myalgia. She was hospitalized for 4 days with the diagnosis of acute myositis due to myalgia and elevated serum creatine phosphokinase levels (CK). Metabolic screening was normal. There was no heart involvement. Pulmonary function tests were in normal limits. Muscle biopsy revealed dystrophic changes and alpha dystroglycan deficient fibers. CK levels were severely elevated (4000-6000 IU/l) after discharge. A pathogenic mutation (c.826 C > A (p.Leu276ıle) (p.276I)) was identified in FKRP gene which is previously unreported. Mutations in the FKRP gene can cause different types of muscular dystrophy-dystroglycanopathy. One of these is an autosomal recessive LGMD type C characterized by variable age at onset, normal cognition, and no structural brain changes. This LGMD2I patient with FKRP mutation reminds muscle pain mimicking myositis as a clinical clue for diagnosis with an unusual symptomatology.

## A novel mutation in FKTN related to alfadystroglycanopathy

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Dystroglycanopathies are genetically heterogeneous group of muscular dystrophies with autosomal recessive inheritence, presenting with a broad spectrum of phenotypes. Here, we present a patient with a novel mutation in fukutin (FKTN) gene. We report an 18-month-old girl of consanguineous parents who presented with inability to sit and walk. Neurological examination showed mild facial, proximal and distal muscle weakness in addition to macroglossia, hypotonia and decreased deep tendon reflexes. The patient achieved a sitting position without support but soon lost position by falling forward or sideways. Eye examination was within normal limits. Serum creatine kinase (CK) was 2500-3000 IU/l on repeated tests. Muscle biopsy showed dystrophic changes. Cranial MRG revealed brainstem and vermian hypoplasia, cerebellar cysts and dysplasia. Genetic analysis showed the homozygous mutation in FKTN (c.1268A > G (Tyr423Cys)) which has not been previously reported. The FKTN gene encodes a type II transmembrane protein that is targeted to the Golgi apparatus through an N-terminal signal anchor. Mutations in the FKTN gene can cause three different forms of muscular dystrophy-dystroglycanopathy such as Fukuyama CMD, Walker-Warburg syndrome, or muscle-eye-brain disease and a less severe congenital form without mental retardation; and a milder limb-girdle form (LGMD2M). Here, we present a patient with a new allelic variant in FKTN gene. The patient has a clinical phenotype milder than FCMD, more severe than LGMD2M that enrich clinic genetic correlations.

## Homozygous POMT1 mutation in a girl with congenital muscle dystrophy with mental retardation

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Mutations in protein O-mannosyltransferases (POMTs) cause a group of neuromuscular conditions ranging in severity from Walker-Warburg syndrome, congenital muscular dystrophy and congenital muscle dystrophy with mental retardation to limb girdle muscular dystrophy. We report a 17-year old female with delayed mental and motor development, elevated creatine kinase level, thoracolumbar scoliosis and calf hypertrophy. It was showed a homozygous mutation c.598G > C in POMT1 gene. In conclusion, we report a case of genetically confirmed musculer dystrophy-dystroglycanopathy (congenital with mental retardation) type B, 1 due to mutation in POMT1 gene.

## A case of muscular dystrophy-dystroglycanopathy type A, 14 with compound heterozygous gmppb mutation

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GDP-mannose pyrophosphorylase B (GMPPB) catalyzes the formation of GDP-mannose, which is required for the glycosylation of lipids and proteins. The clinical spectrum of dystroglycanopathies due to defects in GMPPB varies from muscle-eye-brain/Fukuyama congenital muscular dystrophy-like disease to adult-onset limb-girdle muscular dystrophy with normal cognition. The association muscular dystrophy-dystroglycanopathy and epilepsy has been reported very rarely. We report a case of muscular dystrophy-dystroglycanopathy with a distinctive phenotype characterized by global developmental delay, microcephaly, cerebellar hypoplasia, feeding difficulties, and epilepsy in which EEG showed burst-suppression pattern. Firstly, she presented to our clinic with poor head and neck control and no follow object at age for 4 months. After 2 months she presented with seizures. Her prenatal, natal and family history was unremarkable, and she was born of nonconsanguineous marriage. She had two healthy sisters. On physical exam, she showed weak cry, difficulty in swallowing, axial hypotonia and muscle weakness. No acquired any milestone. Cognitive development was significantly retarded with absent speech. At latest neurological examination, she had microcephaly, muscle wasting, hypotonia and was able to perform head and neck control and distal subgravity movements. Ophthalmologic examination was normal. Karyotype analysis and routine metabolic tests were normal. Cranial magnetic resonans imaging showed cerebellar and vermian atrophy. Whole exome sequencing was performed and identified compound heterozygous GMPPB mutation (c.940G > A (p.V314M) (p.Val314Met)/c.860G > A (p.R287Q) (p.Arg287Gln)) in the our case. For reason of difficulty in swallowing, she was fed via the nasogastric tube and then gastrostomy. Her EEG was within normal limits during the initial presentation at the age of 4 months, on follow up burst-suppression was developed at the age of 9 months. Her seizure types were similar to malign migratory epilepsy and refractory to multiple antiepileptic drugs and pyridoxine. Due to recurrent pulmonary infections, she was followed and treated with intensive care many times. In this periods, rhabdomyolysis episodes developed, creatine kinase levels were between 80-15.000 U/L. She died at the age of 24 months due to acute respiratory infection. In conclusion, this case suggests that GMPPB defects in alpha-dystroglycanopathy may

play a role in the neuronal membrane channels or networks involved in the pathophysiology of epilepsy.

### Merosin-deficient congenital muscular dystrophy: a homozygous mutation in the laminin-2 gene

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*Introduction.* A loss of merosin due to LAMA2 mutations causes merosin-deficient congenital muscular dystrophy which is one of the most common forms of congenital muscular dystrophy. We herein report the case of a patient with merosin deficiency caused by a homozygous mutation in LAMA2. Case report Thirteen month-old male patient presented with delayed developmental milestones. He was the first child of healthy consanguineous parents, was born full term after an uneventful pregnancy. A neurological examination revealed muscle weakness. He could not walk unaided. He was able to control his head at 4 months and sit without support at 9 months. Deep tendon reflexes were absent. His serum creatine kinase level was 2275 U/L. Brain magnetic resonance imaging showed hyperintensity on T2-weighted images. A subsequent biopsy of gastrocnemius showed a loss of merosin staining, indicating a loss of merosin protein. Mutation screening of LAMA2 was performed. We found a homozygous mutation of LAMA2, c.4524-2A > T. Discussion Merosin-deficient congenital muscular dystrophy is diagnosed on the basis of clinical presentations, including hypotonia, high serum creatine kinase levels, white matter alternations, as well as deficiency of merosin expression in biopsied muscle and homozygous mutation in LAMA2. We describe a LAMA2 homozygous sequence variant in a patient with merosin-deficient congenital muscular dystrophy.

### Ullrich muscular dystrophy presenting with hyperlaxity

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*Objective.* we aim to describe the patient presenting with hyperlaxity who has diagnosed Ullrich muscular dystrophy. Method: we examined patients medical reports. We evaluated patient's age, family history, consanguinity, physical examination findings, laborotuary parameters from medical reports. Results: the subject is four years old and female. She was refered to us with muscle weakness, hyperlaxity, developmental delay. Parents had second degree relatives. She was born with vaginal delivery at 38 gestastional weeks. In the first day of life she had respiratuary distress and feeding difficulties. She had monitored in neonatal intensive care unit for seven days. Then her developmental milestones were delayed. In the first visit, she was 18 months and she was able to sitting with support and she couldn't stand. She was moderately hypotonic. She had joint and skin laxity and prominent thoracic scoliosis. Deep tendon reflexes were hypoactive. Creatin kinase level was mildly elevated (ck: 750 U/L) and except ck level, there is no abnormality in other serum biomarkers. Brain magnetic resonans imaging was normal. All these findings we examined COL6A1 gene and there is p.G512S (c.1534G > A) heterozygous mutation. This mutation was commented as clinical unknown significance in genetic databases. Conclusion: Ullrich congenital muscular dystrophy(UCMD) corresponds to the severe end of clinical spectrum of neuromuscular disorders caused by mutations in the genes encoding collagen VI. Clinical manifestations of UCMD are muscle weakness, proximal joint contractures, distal hyperlaxity and normal intelligence. This disorder was identified as a rececssive condition with homozygous and compound heterozygous mutations in COLVI gene. Over the last few years, some patients peresenting with clinical manifestations of severe UCMD were shown to carry heterozygous mutation in these genes which acquired as dominant de novo. UCMD should be considered in the differential diagnosis the patient who was presenting with developmental delay, muscle weakness and hyperlaxity.

### COL6A2 related Ullrich congenital muscular dystrophy associated with epileptic encephalopathy

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*Objective.* Collagen-VI related myopathy has a broad clinical spectrum and is caused by mutations in the three collagen-releated genes (COL6A1, COL6A2 and COL6A3). Both dominant and recessive mutations may underlie the entire phenotypic spectrum of these myopathies. The relationship between COL6A2 gene mutation and epilepsy has not yet known. Here, we presented 3 years old boy, who is followed with a diagnosis of epileptic encephalopathy and is identified of COL6 gene mutation. So we aimed to discuss the relationship between COL6A2 gene and epilepsy.

*Method.* Three year-old boy presented with psycho-motor retardation at the age of 8 months. The prenatal, natal and early postnatal periods of the patient were uneventful. He was born at term with normal height and weight. Parents were consanguineous. Cranial magnetic resonance imaging showed T2 hyperintens areas at the deep white matter and cortical atrophy. Refractory epileptic seizures occured at the age of 18 months and his EEG patern was compatible with Lennox-Gastaut Syndrome. Physical examination showed axial hypotonia, hyperextansibility at ankle and wrist joints, tension in achilles and hamstring tendons and increased DTR. He could not hold his head and sit unsupported. He had eye contact but can not speak. Results: Whole exome sequencing showed homozygous c1531G > A, (p.Gly511Ser) mutation in COL6A2 gene. This mutation confirmed with Sanger sequencing. The clinical phenotype was compitable with Ullrich congenital muscular dystrophy. Conclusion: It is controversial whether the accompanying epileptic encephalopathy is associated with the COL6A2 gene mutation in our case with diagnosis Ullrich CMD. The fact that the COL6A2 gene mutation has been reported in two brothers with progressive myoclonus epilepsy in the literature suggests a relationship between COL6A2 gene mutation and epileptic encephalopathy.

### A spectrum of laminopathies: Pandora's box

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*Objective.* A wide spectrum of diseases called "laminopathies" is linked to defects in genes encoding lamin A/C (LMNA), and B-type lamins (LMNB1, LMNB2).

*Methods.* We reviewed 9 patients from 7 unrelated families with heterozygous mutations in LMNA (6 non-consanguineous Turkish families), and homozygous mutation in LMNB2 (1 consanguineous Arab family). Molecular diagnosis was through targeted analysis to LMNA (n = 5), neuromuscular gene-panel (n = 1), and WES (n = 1). Results: Mean age of patients (3 girls, 6 boys) was 6 years (18 months-10 y). Mean age at onset of symptoms, and evaluation was 10.6 months (newborn period - 3 years), and 26.7 months (0-6 y), respectively. Presenting symptoms were; axial hypotonia (n = 7), asymptomatic elevated CK (n = 1), truncal ataxia, impairment of walking and seizures (n = 1). Independent walking was achieved by 2 years of age in 7/9. CK was elevated in 8/9 (range 450-1900 U/L). Muscle biopsy showed nonspecific myopathic and dystrophic changes (n = 4). All patients had normal cardiac evaluation at presentation. During a mean follow-up duration of 33.5 months (0-6 y), one patient developed cardiac hypertrophic changes and required noninvasive nocturnal mechanical respiratory support after the age of 8 years, another patient had tricuspid valve insufficiency and pulmonary hypertension at 5 years, and died 10 months later with a sudden seizure and respiratory insufficiency. Conclusions: Gained independent walking despite head-lag, increased CK levels were clues for LMNA mutations. Beyond well-known phenotypes, early ataxia, developmental delay, and seizures may be clues for LMNB2 mutation. Cardiac and respiratory features need close monitoring.

### SEPN1-related congenital myopathy: a case report

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Selenoprotein-N, which is encoded by SEPN1gene, is an endoplasmic reticulum glycoprotein. To date, SEPN1mutations have been associated four autosomal recessive myopathies: rigid spine muscular dystrophy, multiminicore disease (classical form), desmin-related myopathy with Mallory body-like inclusions and congenital fiber-type disproportion myopathy. Although morphological differences exist, clinical findings are similar.

The typical patient has early onset weakness that primarily affects the axial skeleton, develops scoliosis, rigid spine, in addition to respiratory insufficiency and relatively preserved limb muscle strength. We reported a patient with of respiratory failure in early childhood unrelated to limb weakness.

*Case report.* A 10-year-old girl presented with retardation in growth and development, difficulty in walking and climbing stairs since 3 years old. Parents were consanguineous. On the neurological examination; there were myopathic facial appearance, scoliosis, scapular winging, rigid spine finding and positive Gowers sign. Deep tendon reflexes were absent. Muscle strength was 3/5 in upper and 4/5 in lower extremities. In general, all muscles showed atrophy. Elbow laxity was present but no contracture was observed. Creatine kinase level was normal. Nerve conduction studies were normal in electroneuromyelography. Needle electromyelography examination revealed myogenic involvement accompanied by denervation in the proximal and distal muscles. Echocardiography was normal. In muscle biopsy, nonspecific myopathic changes were observed. The homozygous c.817G > A (p.G273R) mutation in the SEPN1gene was detected. The diagnosis was with SEPN1-associated congenital myopathy. She has needed nocturnal respiratory support for the last 1 year.

*Discussion.* Selenoprotein-N is expressed in many tissues, such as the skeletal and heart muscle, the lung. Although the precise function of SEPN1 protein is uncertain, recent studies suggest a role in cell protection against oxidative stress. The development of respiratory failure is not related to skeletal weakness. Progressive deformity of the spine is observed during childhood. Early respiratory failure may be a clue for this type myopathy.

## Session 3. Peripheric neuropathies and myasthenia

### Autosomal recessive charcot-marie-tooth disease in a turkish boy due to a novel homozygous mutation in ighmbp2 gene

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*Objective.* Charcot-Marie-Tooth (CMT) disease is clinically and genetically heterogeneous disease,and mutations have been reported in at least 80 genes. In 2014, a mutation in Immunoglobulin helicase μ-binding protein 2 (IGHMBP2) gene which is responsible for spinal muscular atrophy with respiratory distress type 1 (SMARD1) was found to cause CMTdisease type 2S. Method We report a 10-year-old Turkisch boy with CMT symptoms including foot-drop gait, running difficulties, frequent falls, progressive atrophy of lower legs with a prominent foot deformity. No family history of similar problems was presented. Nerve conduction studies suggested axonal predominant sensorimotor polyneuropathies. Roche MagNA Pure Compact system was used to isolate DNA from whole blood of the patient and quantified by using NanoDrop spectrophotometer. Illumina TruSight Inherited Disease pane and MiSeq Next-Gen system were utilized to screen 552 genes for mutations related to AR pediatric-onset diseases. Data were analyzed on Illumina VariantStudio data analysis platform. Results Our results demonstrated homozygous NM_002180.2 (IGHMBP2):c.2080C>T (p.Arg694Trp) mutation. Arg694Trp mutation was localized to single-strand DNA binding domain of the protein and alters the structural and functional properties. Considering previous studies exploring the mutations in IGHMBP2 and CMT2 the patient was diagnosed as CMT2. This mutation was not previously reported Conclusion: To the best of our knowledge, this report is the first of a Turkish patient with IGHMBP2 gene-related CMT. Since the number of consanguineous marriages is high in Turkey, mutation screening of IGHMBP2 should be especially considered in AR-CMT2 and sporadic CMT2 patients.

## Novel mutation in PLEKHG5 causes autosomal recessive Charcot Marie tooth disease

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We present a Turkish girl diagnosed as autosomal recessive, intermediate Charcot Marie tooth disease type C (CMTRIC) with a novel mutation in PLEKHG5 gene. An 8 years old girl was admitted with the complaint of frequent falls and difficulty in climbing stairs since last year. Neurologic examination revealed limb girdle muscle weakness, and absent deep tendon reflexes. While she could barely walk on the fingers and heels, she had more obvious difficulty standing up from sitting position. Neuropathic changes like atrophy were not observed. Creatine phosphokinase levels measured at different times were 489 and 639 IU/l, respectively. The electromyelography was consistent with axonal neuropathy. Metabolic tests, genetic analysis in terms of spinal muscular atrophy, and thigh magnetic resonance imaging were normal. Muscle biopsy showed secondary neurogenic changes. A novel homozygous mutation in the PLEKHG5 gene was detected in whole exome sequencing as c.1561-2A > G (IVSI4-2A). Autosomal recessive CMTRIC is caused by homozygous or compound heterozygous mutation in the PLEKHG5 gene on chromosome 1p36. First description was made by Azzedine and Kim et al. in 2013. To date, 20 different variants associated with the PLEKHG5 gene have been identified. This novel mutation will contribute to the literature in terms of genotype phenotype correlation.

## Charcot Marie tooth disease type 2n: a case report

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*Introduction.* Charcot Marie tooth disease (CMT) is one of the most common neurogenetic diseases is classified into various subgroups by clinical, electrophysiological, histological, genetic findings. CMT2 is characterized by dominant transient axonal neuropathy. Mutation in the alanyl-tRNA synthetase (AARS) leads to CMT2N, that is rarely reported in 4 families so far.

*Case.* A 6.5-year-old girl was admitted to our clinic with frequent falls, unsteady walking. She hold her head steady at 4 months, sat without support at 10 months, walked byself at 2 years old. There was relationship between the parents. Physical examination of the cranial nerves revealed normal. There was no myopathic facial appearance, but was minimal scoliosis to the left. Deep tendon reflexes were taken bilaterally. Gowers sign was negative. Clinical features also included steppage gait, pes cavus, bilateral genu valgus deformity and tenar-hypotenar atrophy. EMG revealed polyneuropathy with mild demyelination. PMP 22 gene for CMT Type 1 was identified as normal, and a new heterozygous mutation in the AARS gene was detected with new generation sequencing. These changes were found to be consistent with CMT axonal type 2N.

*Discussion and conclusions.* AARS is a cytoplasmic protein localized to 16q22.1. The deficiency is caused by autosomal dominant axonal neuropathy. The disease may begin between the ages of 6 and 54, usually with slow progression. Patients can stay ambulatory until the end of their lives. Significant weakness and mild atrophy in distal extremities, pes cavus, hammer finger may develop. Sensorineural hearing loss has been reported in some cases. Mutations in 15 genes/loci have been identified to cause either autosomal-dominant or -recessive CMT2. These hereditary neuropathies have a variable degree of severity and a wide range of clinical manifestations. This phenotypic variability can sometimes be seen in affected members of the same family. The early diagnosis is possible with carefully examination of patients.

## Hereditary neuropathy with glypican 1 gene mutation

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*Introduction.* The hereditary forms of peripheral neuropathies include a large group of genetic diseases. More than 100 genes have been involved. Since the clinical presentations of all polyneuropathies overlap clinican should make distinction between immune-mediated and idiopathic forms.

*Case presentation.* A patient with normal neurological development had complaints of frequent falls at 4 years of age. The patients EMG reveiled polyneuropathy affecting predominantly lower limbs. The patient was diagnosed as CIDP and recovered after treated with steroid therapy. But cessation of steroid therapy caused relaps and retreatment was not effective. Because of consanguinity genetic investigation performed revealing homozygous Glypican 1 mutation.

*Discussion.* Next generation sequencing–based testing to diagnose genetic disease has become part of routine clinical practice in the meantime. The simultaneous analysis of many neuropathy genes is logical and we reveiled a glycan 1 mutation in this way.

Glypican 1 protein is specifically expressed in the anterior horn motor neurons, dorsal root ganglia and commissural neurons. It is known to be a co-receptor involved in the crossing and progression of axons during neuronal development. Mouse knockdown models reveiled defective axonal development.

*Conclusions.* Genetic research should be done in terms of hereditary causes in case of treatment-unresponsive CIDP. This patient is the first case where the glycan 1 mutation has been shown and this mutation should be sought when investigating hereditary causes.

## Fazio Londe syndrome

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Fazio Londe syndrome is a rare neurological disorder presenting with progressive bulbar palsy with respiratory failure. Mutations in the SLC52A3 gene cause a defect in intestinal riboflavin transport (hRFT2). Supplementation of riboflavin is a lifesaving treatment especially for young patients. We report a 14-year-old girl presented with inability to close eyes, difficulty in swallowing and voice change since 12 year of age. Physical examination showed lower motor neuron facial nerve palsy, tongue atrophy and fasciculation, limb wasting and dysphonia. Genetic testing (whole exom secans) confirmed the diagnosis of

Fazio Londe syndrome. We started riboflavin 10 mg/kg/day supplementation. Now there is a slow progression in the patient. She comes to our clinic every 3 months. Her mother said that their cousins had similar complaints. But they live in Irag for that reason they don't come for family members screen. In any child who presents with progressive bulbar palsy and lower motor neuron facial palsy a diagnosis of Fazio Londe syndrome should be considered and family members should also be screened.

## Neuromyositis: a case report

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*Purpose.* To draw attention to association of peripheral nerve and muscle involvement.

*Introduction.* Peripheral nerve involvement in polymyositis and dermatomyositis has been known since 1893. It is called neuromyositis. Vascular abnormality in small veins is thought to cause it. Electrophysiological characteristics of polyneuropathy are distal and axonal damage observed more in lower extremities.

*Case.* A 76 year old male patient applied with complaints of loss of strength in legs and skin rashes. He said that loss of strength started in both lower extremities for about the last 3 months and rashes and peeling in the body for the last 15 days. He applied to our clinic when the complaints increased.

Conscious, cooperative, oriented, papillary isochoric in the eye sphere mid line, light, corneal reflex was bilaterally positive. Cranial nerve examination was normal, muscle strength was 3-4/5 in both lower and upper extremity proximals and 0-1/5 in both lower extremity distals.

DTR was not obtained in all four extremities. Pathologic reflex was absent. There was stoking-glove like sensory disorder and butterfly like rashes in the face and rashes in the inner side of both elbows and in both knees. Dermatology consultant physician verified the diagnosis of the patient as dermatomyositis. CK level was 1654.

ENMG was applied to the patient, and in the lower, more apparent findings coherent with sensoriomotor polyneuropathy, and short term polyphasic MUPs which suggested myogen involvement were observed in the needle EMG. The patient was considered dermatomyositis under the light of available clinical and laboratory findings. Biopsy was taken from the left deltoid muscle. Infarct areas, endo and perineural inflammation were observed in muscle tissue.

*Conclusions.* DM is a muscle disease in which necrosis/regeneration, perivascular infiltration of mononuclear inflammatory cells and intramuscular vasculitis play a role in the muscle fibers. Recent findings suggest that this is caused by an immune response with humoral intermediary in which these inflammatory cells, B cells with immune intermediary, especially antibodies in circulation and immune complexes, take part.

## Three patients with congenital myatenic syndrome

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*Objective.* The congenital myasthenic syndromes (CMS) are a diverse group of genetic disorders caused by abnormal signal transmission at the motor endplate, a special synaptic contact between motor axons and each skeletal muscle fibre. Most CMS stem from molecular defects in the muscle nicotinic acetylcholine receptor.

*Method.* Three patients who have applied to İnönü University Department of Pediatric Neurology diagnosed with CMS have been evaluated.

*Results.* Two of our patients were male and one was female. Our patients who were taken to study were followed up with muscle disease. Cranial MRI and metabolic examination were normal. The genetic result of our patients revealed two mutations of COLQ and one SCNA4A mutation. According to the results of the mutation, the ephedrine started and the clinical improvement was observed.

*Conclusions.* Congenital myasthenic syndrome is a rare muscle disease. Genetic analysis is important because congenital myasthenic syndrome treatment can vary according to the cause of the mutation.

## Antibody levels in myasthenia gravis patients

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*Introduction.* Juvenil myasthenia (JM) is an autoimmune disease in which the neuromuscular component is damaged by antibodies and the frequency is reported to be 2-10 at 100.000. Among myasthenia autoimmune neurological disease, antigen, antibody and pathogenesis are the best known. Antibody response can beclassified according to antigen targeted: acetylcholine receptor (aChR), muscle-specific kinase (MuSK), lipoprotein receptor-associated protein4 (Lrp4). In most cases aChR antibodies are detected. Material and Method In Hacettepe University Faculty of Medicine Department of Pediatric Neurology from January 2010 to November 2017 were reviewed JM patients aged between 2 and 18 years retrospectively. Demographic data were obtained from clinical-laboratory data files. A total of 50 patients diagnosed as JM were divided into seropositive and seronegative groups according to their serum antibody levels and their clinical characteristics and treatment responses were evaluated. The researche data was uploadede and evaluated in the computer programme "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)".

*Results.* A total of 48 patients (96%) were evaluated for aChR antibodies. Of these, 27 (56.3%) patients were seropositive and 21 patients (43.7%) seronegative. The aChR antibodies positivity rate in the generalized JM was 70.6% and in the ocular group was 50%. The positivity rate of anti-MuSK antibodies was 0% in the generalized group and 80% in the ocular involment group. Six of 12 patients (50%) were positive for the serum anti-MuSK antibody. The number of patients with both antibodies (aChR and anti-MuSK) negative was 5 (10% of total patients).

*Discussion.* Anti-MuSK positive patients had relatively local ocular and ocular-bulbar involvement. AchR antibodies patients showed generalised involvment. Double seronegative patients accounted for 10% of total patients. In this double negative patients group showed generalized muscle involvment. The characteristic feature in this group was drug resistants and require immunosupresive treatment.

*Conclusions.* The seronegative group in JM patients may show diffuse involvment and resistance to anticholinesterase and steroid treatments; other treatment options must be considered.

### Our experience of rituximab in two cases with anti-musk positive myasthenia gravis refractor to steroid and intravenous immunglobuline

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*Objective.* Anti-MuSK positive myasthenia gravis is a rare condition in childhood. Unlike other seropositive myasthenias, its course is more severe with facial and bulbar weakness and respiratory distress. The response to conventional immunotherapy (steroids and IVIg) is usually not good. We aimed to share our experience with rituximab treatment in two cases with anti-MuSK positive myasthenia gravis who had bulber involvement and did not well respond to IVIG and steroid therapy.

*Method.* A 4-year-old girl and a 14-year-old boy, who were from different families, were brought with ptosis, fluctuating muscle weakness, swallowing and breathing difficulties induced by exercise. Physical examination showed more pronounced weakness in facial muscles, bulbar muscles, deltoid, triceps, and iliopsoas muscles, there was no weakness in distal muscles, and deep tendon reflexes were normal. The rest of the physical examinations were normal.

*Results.* In both cases, EMG study revelaed decremental response with consecutive nerve stimulation. Anti-AchR antibody was negative, and anti-MuSK antibody was positive in both patients. There were no response to IVIG and steroid treatments, respectively. Rituximab was ordered 4 doses, 375 mg/m2/dose weekly, and significant clinical improvements were observed. Steroid and cholinesterase inhibitor treatments were discontinued, respectively.

*Conclusions.* In the cases of anti-MuSK positive myasthenia gravis who do not well respond to steroids and intravenous immunoglobuline, rituximab therapy should be tried without losing time considering the severe course of the disease.

## Session 4. Methabolic disorders

### Rare causes of rhabdomyolysis: lipid storage myopathy and McArdle disease

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*Objective.* Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. Creatine kinase (CK) levels are typically markedly elevated, and muscle pain and myoglobinuria may be present. The lipid storage myopathies and McArdle disease represent a small percentage of the cases of rhabdomyolysis.

*Method.* Electronic medical records of 188 patients from our neuromuscular clinic were analysed. Nine patients were diagnosed with rhabdomyolysis. Clinical findings, laboratories, electrophysiological tests and muscle biopsy results were investigated. Results. Among 9 rhabdomyolysis patients, 2 patients were diagnosed with lipit storage myopathy. The first patient was 21 years-old and had congenital ptosis, muscle pain, weakness, dark urine and elevated CK levels. The second patient was 31 years old and represented with muscle pain, cramping, dark urine and elevated CK levels. McArdle disease was confirmed in 3 patients. The patients with myophosphorylase deficiency were 21, 36 and 48 years-old. They were represented with exercise intolerance, fatigue, myalgia, cramps, poor endurance, muscle swelling, and fixed weakness symptoms. In the other 3 patients, the types of myopathies couldn't be clarified. 1 patient refused muscle byopsy.

*Conclusions.* This report illustrates 2 early-onset cases of lipid storage myopathies and 3 patients with McArdle disease. These metabolic myopathies should be considered in the evaluation of patients with nontraumatic rhabdomyolysis.

### Late onset glutaric aciduria type II: think treatable!

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*Case presentation.* A previously healthy 10-year-old boy presented to our clinic with exercise intolerance and proximal muscle weakness. He developed difficulty climbing up the stairs and fatigue within two months. He was evaluated in another center; electromyography, lumbar magnetic resonance imaging (MRI) studies were normal. He had a cranial MRI demonstrating Arnold-Chiari type II malformation. He was treated with intravenous immunoglobulin with a final diagnosis of Guillain-Barre syndrome. There was no rash, unexplained fever, malaise and weight loss during this period. The course of the disease was mildly progressive.

Parents were first cousins. His mother had a diagnosis of ankylosing spondylitis, and his sister had a diagnosis of rheumatoid arthritis.

On physical examination his proximal muscle strength was 4/5 according to the MRC scale. There was no muscle hypertrophy. Modified Gower's sign was noted when arising from a seated position. Deep tendon reflexes were normal.

Serum creatine kinase level was 922 U/L (n = 55-215 U/L), tandem mass spectrometry and urinary organic acid profile had signatures of glutaric aciduria type II. Muscle biopsy evaluation was consistent with lipid storage myopathy. Combined treatment with CoQ10 supplementation and riboflavin is started immediately. Further targeted analysis of ETFDH resulted in a homozygous 1130 T > C (L377P) mutation.

*Conclusions.* Previous diagnosis, laboratory evaluations, treatment and family history can be distractive. Combining history, physical examination, biochemical and muscle biopsy findings is critical to have a final diagnosis on the bedside. Recognition of these signatures leads to timely diagnosis of late-onset riboflavin responsive multiple acyl-CoA dehydrogenase deficiency (MACD), glutaric aciduria type II.

### Exercise induced muscle stiffnes: brody myopathy

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*Introduction.* Brody myopathy is a rare inherited myopathy due to a diminished sarcoendoplasmic reticulum Ca + 2 ATPase 1 activity caused by mutations in ATP2A1.

*Case.* A 13-year-old boy presented with exercise-induced muscle stiffness and cramps since early childhood. His symptoms were worse on cold weathers. There was no history of episodic muscle weakness and rhabdomyolysis. He was born at term with no complication. His psychomotor development was normal. The parents were consanguineous. Neurologic examination revealed normal muscle strength and deep tendon reflexes. Serum creatine kinase value was 437 IU/L. There was no myotonia in his hands but forced contractions of eye lids showed delayed muscle relaxation suggesting paradoxal myotonia. Needle examination did not show myotonia in limb muscles but ocular muscles showed complex repetitive discharges after repeated contractions. Examination of SCN4A gene for paramyotonia congenita showed no mutations. Whole exome sequencing showed a homozygous mutation in the ATP2A1 gene.

*Discussion.* The main finding of Brody myopathy is exercise-induced muscle stiffness which involve predominantly legs, hands, arms and eyelids. Symptoms resolve within a few minutes of rest, may worsen in the cold. Frequently mimics paramyotonia congenita. Serum creatine kinase level is normal or slightly elevated. The main symptoms in our case was exercise-induced stiffness and serum creatine kinase value was slightly elevated. Nerve conduction studies are normal and needle electromyography may show myopathic changes. Although myotonic or complex repetitive discharges have not been reported in Brody myopathy, the patient had complex repetitive discharges in ocular muscles after repeated contractions. Brody myopathy is transmitted as an autosomal recessive or dominant trait. The recessive inheritance is associated to the mutation of the ATP2A1. There is no specific therapy but dantrolene and verapamil may improve exercise tolerance.

*Conclusions.* Brody myopathy should be suspected in cases with exercise-induced delay in muscle relaxation, myalgia and muscle cramps.

## Leigh syndrome with ptosis: a case report

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*Objective.* Mutation in the COX assembly factor 1 (SURF1) is one of the nuclear mutations consistently associated with Leigh syndrome (LS). Optic atrophy, pigmentary retinopathy and strabismus were the most frequently observed ophthalmologic manifestations whereas ptosis less often. We report a case presenting with acute reversible bilateral ptosis later diagnosed LS.

*Case.* A 14-month-old girl presented with one-week history of bilateral ptosis. Brain Magnetic Resonance Imaging showed bilateral symmetric T2A hyper intensity signals in the substantia nigra, subthalamic nucleus and muscle biopsy were suggestive for COX deficiency with SURF1 mutation. We recognized remarkable recovery of ptosis after management of high dose vitamin and coenzyme Q10 treatment. Genetic analysis of the SURF1 gene revealed a homozygous deletion. We have evaluated our patient showed remarkable clinical improvement at first attack but it could not stop progression of neuropathological lesions and clinical deterioration.

*Conclusions.* Patients with LS may present with only ptosis as an initial presentation, symptoms may begin at any age and be the sole manifestation particularly at onset of the disease. Despite the progress in the management of patients with LS, the long-term morbidity remains poor.

## A case of small fiber neuropathy: fabry disease

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*Introduction.* Small fiber neuropathy is detected in 72-77% of cases with Fabry disease. Although presence of angiokeratoma is a very helpful finding, the diagnosis of Fabry disease is often delayed.

*Case.* A 23-year old male was referred to our neuromuscular clinic from dermatology with burning of all of his distal limbs. In addition to this discomfort he had episodes of pain often lasting from several hours to one day. These complaints were started at childhood and similar complaints were also present in his mother and aunt. Neuropathic pain was poorly controlled despite numerous attempts at treatment with analgesics. Physical examination revealed numerous angiokeratoma. Neurological examination was normal. There was no dysautonomia and trophic skin changes. Extensive investigations for small fiber neuropathy were normal including complete blood count, antinuclear (ANA), extractable nuclear (ENA) and antineutrophilic cytoplasmic (ANCA) antibodies. Motor and sensory nerve conduction studies and needle electromyography were normal. RR interval variation test and sympathetic skin responses were also normal. Analysis of his leukocytes revealed low alpha-galactosidase activity and molecular genetic investigations showed homozygous mutation of c.[1025G > A]. In family screening, the same mutation was also detected in his mother and aunt.

*Discussion.* This case highlights the prior consideration of fabry disease in patients with angiokeratoma and small fiber neuropathy.

## Association between muscle cramps, fatigue, pain and Serum 25-(OH) vitamin D levels in myotonic patients

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*Aim.* The aim of this cross sectional retrospective study was to evaluate the association between muscle cramps, fatigue, pain and Serum 25-(OH) vitamin D levels in myotonic patients.

*Material and methods.* The clinical data obtained from the patients' files were evaluated. The demographic and socioeconomic status of all patients were recorded. Functional levels were determined by functional ambulation classification (FAC). The muscle cramps, fatigue and pain symptoms which were questionned before were evaluated. Serum 25-(OH) vitamin D levels previously measured and recorded in the patient file were evaluated. Deficiency of vitamin D was defined as ≤ 20 ng/ml, insufficiency 21-29 ng/ml and normal level ≥ 30 ng/ml.

*Results.* There were 53 patients with a mean age of 31,13 ± 15,32 (5-63) years and duration of illness was 8,38 ± 6,61 years. There were 34 patients diagnosed with myotonic dystrophy, 13 patients diagnosed with myotonia congenita and 6 patients diagnosed with myotonia. 75,5% of patients was FAC level 4 and above. The percentage of patients who were non ambulators was 11.3%. The mean 25-(OH) vitamin D level

was 14.45 ± 7,29 ng/ml. Forty-three (81.1%) of patients had vitamin D deficiency. There were 30 patients who complained of muscle cramps, 34 patients complained of fatigue and 8 patients had pain. There was no significant difference in vitamin D levels between the patients with cramp, fatigue and pain and the patients without cramp, fatigue and pain ($p > 0.05$). Conclusion. Our study demonstrates that vitamin D are not associated with muscle cramps, fatigue and pain in myotonic patients, which needs to be confirmed in future studies.

## Awareness and knowledge level of osteoporosis in patients with neuromuscular diseases-multicentre study

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*Objective.* We aimed to evaluate the awareness and knowledge level of osteoporosis in patients with neuromuscular diseases.

*Material and methods.* A total of 48 adult and 60 child patients (74 m, 34 f) were included in the study. The demographic and socioeconomic status of all patients were recorded. Functional levels were determined by functional ambulation classification, vignos and brooke scales. Participants (adult and child's parents) were completed a questionnaire assessing their awareness of osteoporosis and measuring their knowledge using a 30-item instrument.

*Results.* The mean age of patients was 22.78 ± 19.20 (1.5-76) years and duration of illness was 7.44 ± 8.72 years. 30.6% of patients was vignos level 4 and above. Also 89.8% of patients was brooke level 3 and below. The percentage of non ambulators patients were 18.9% and independent ambulators were 30.6%. Awareness osteoporosis of parients and adult patients were 93.3% and 97.9% respectevely. However the knowledge level points of patients were 12.78 ± 6.38 (0-30).

*Conclusions.* While there is high awerness of osteoporosis in patients with neuromuscular diseases, knowledge level of osteoporosis is very low in these population.

## A rare cause of neuropathy: Andermann syndrome

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*Introduction.* Agenesis of the corpus callosum with peripheral neuropathy or Andermann syndrome is a rare autosomal recessive disorder characterized by progressive motor and sensory neuropathy, variable agenesis of the corpus callosum (ACC), mental retardation and dysmorphic features. The disorder appears early in life with delayed developmental milestones. Patients have an axonal type severe motor-sensory polyneuropathy with areflexia. A total or partial ACC is detected by cerebral MRI. SLC12A6 is the only gene associated with Andermann syndrome, which encoded the K-Cl cotransporter KCC3.

*Case report.* A 2-year-old boy was admitted because of developmental delay. He was born through vaginal delivery at 38 weeks gestation after an uneventful pregnancy with consanguineous parents. The birth weight, height, head circumference was normal. Physical examination showed mild psychomotor retardation, diffuse hypotonia and weakness in lower extremity. Deep tendon reflexes were absent. There were no dysmorphic features. Cranial MRI showed total agenesis of the corpus callosum. Electrodiagnostic studies showed slowness of motor nerve conduction velocities. Sensory nerve action potentials could not be elicited in the median, ulnar and sural nerves. Mutation in SLC12A6 gene was detected and diagnosed as Andermann syndrome.

*Discussion.* Andermann syndrome is a very rare autosomal recessive disorder associated with mutations in the SLC12A6 gene. The disease was first described in French Canadian population of a distinct region in Quebec. A local founder effect has led to a high prevalence. The disease is rarely reported from Turkey, Italy, The Netherlands, Germany and Africa.

*Conclusions.* Andermann syndrome should be suspected in pediatric cases of delayed developmental milestones, peripheral neuropathy and agenesis of corpus callosum.

## Revisiting infantile neuroaxonal dystrophy (INAD): highlights!

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*Introduction.* INAD is a rare autosomal recessive neurodegenerative disease due to PLA2G6 mutations. The phenotype-genotype relationship is complex.

*Materials and methods.* We retrospectively analyzed clinical, laboratory and neuroimaging findings of 12 patients, in whom diagnosis of INAD is confirmed based on PLA2G6 mutations.

*Results.* There are 4 girls, and 8 boys. Age of the patients ranged between 83-151 months and the age at onset of the symptoms ranged between 11 and 29 months. The patients' average age is 9,7 years in those who are alive. Time between the onset of the symptoms and the diagnosis ranged between 2,5-8 years. Presenting symptoms were; truncal ataxia and hypotonia continued with loss of motor skills, spasticity, and contractures. None of them had epilepsia at the time of the diagnosis and optic atrophy was present on ophthalmological examination in 8 of them. Magnetic resonance imaging revealed cerebellar atrophy by the age of 2 years in all patients and 4 of them showed cerebellar cortical hyperintensity on T2 weighted imaging. Electromyography at the age ranged between 2-5,5 years showed polyneuropathy in 4/8. Four patients died during monitoring, and our oldest surviving patient is 12-years-old currently. Compound heterozygous mutations (n = 3) and homozygous mutations (n = 9) were detected. Patients with compound heterozygote mutations showed more prominent cerebellar system findings and had a milder progressive course.

*Conclusions.* INAD is a rare, rapidly progressive neurodegenerative disease. The phenotype-genotype relationship is complex. Despite recognition of clinical and neuroimaging signatures, there is stil a presentational and diagnostic delay. Hypotonia, truncal ataxia, neurodegenerative course and cerebellar atrophy and hyperintensity are definitely the clues for early diagnosis.

## Frequency of Fabry disease in patients with cryptogenic painful small-fiber neuropathy

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*Background.* Fabry disease (FD) is an X-linked inherited lysosomal storage disorder caused by α galactosidase A (α-gal A) deficiency. Early occurrence of small-fibre neuropathy (SFN) is a common feature of FD. Patients with SFN present with sensory symptoms and pain; the latter is often the dominant symptom. Therefore, we investigated the frequency of FD in patients with painful SFN of unknown aetiology. Methods. Fourteen adults with seemingly idiopathic pure or predominantly small fiber sensory neuropathy were examined for alpha-galactosidase A (α-gal A) activity and/or mutations in the α-gal gene (woman patients) between november 2016 and december 2017. α-gal A activity was measured in dried blood spots (DBS). All patients underwent a standardized focused etiological and clinical investigation before the genetic analysis.

*Results.* Decreased α-gal A leukocyte activity was detected in 1 23-year old male patient. Genetic testing to search for a disease-causing mutation in the gal gene was performed and a typical homozygous mutation for FD c.[1025G > A] (p.[R342Q]) was detected. Among further manifestations for FD, angiokeratoma was found. The same mutation was identified in two other individuals in patient's family.

*Conclusions.* Here we present a FD screening study using DBS method in cryptogenic neuropathy patients. We think that FD should be considered in patients with painful SFN and screening for FD should be included in the diagnostic guidelines for patients with SFN.

## Hyperacute myelopathy: a rare etiology and a good response to an outstanding treatment

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*Objective.* We report a case of teenage patient presenting with acute onset rapidly progressive paraplegia. Our aim is to draw attention to spinal cord infarction(SCI) and fibrocartilaginous embolism (FCE) as a rare and under-recocnized cause of acute myelopathy in children.

*Case.* A 12-year-old girl, otherwise healthy, suddenly felt severe chest pain at the gym class. In 15 minutes, she couldn't step on her feet; after 2-3 hours she was paraplegic. On presentation, her vital signs were normal. Neurologic exam revealed motor force 0/5, with the absence of pain and temperature sensation and deep tendon reflexes in the lower extremities and a distended bladder. In her history, 2 days before she was pushed hardly from back by a friend and hyperextended her neck. Intravenous steroid was started immediately with a presumptive diagnosis of transverse myelitis. Laboratory investigation showed no evidence of infectious, autoimmune, inflammatory, or neoplastic causes. Lumbar puncture was unremarkable. Thrombotic work-up was normal. Spinal MRI revealed increased T2 intensity without swelling or abnormal contrast enhancement at the C7 to T6 level, localized within the anterior spinal cord. It also showed non-compressive C6-7 disc protrusion (T2-hyperintense, presumably acute) coinciding with the segment of the spinal cord findings. There was no clinical response to steroid; plasmapheresis was started on the 5th day, a minimal withdrawal was seen in her legs but no improvement in urinary retention and bowel incontinence. Hyperacute flaccid paralysis beginning with chest pain discussed with neurological findings, no response to steroid and "ischemic myelopathy" was thought; enoxaparin was started. Although no histologic confirmation was obtained; lack of evidence for other ischemic etiologies in the setting of clinical presentation and MRI findings made FCE the most likely diagnosis. With the aim of suppressing the secondary inflammation and further neuronal damage, IVIg and rituximab treatments were started. Slow but consistent improvement was seen by then. One month after this treatment she was walking with one-sided assistance; has no urinary and bowel dysfunction.

*Conclusions.* SCI, because of FCE, is very rare; certain diagnosis is based on the biopsy/autopsy in the literature. There is no well defined treatment. Whatever the etiology of myelopathy, secondary inflammation enhances the cord injury. Intensive treatment of this inflammatory phase associated with neuronal plasticity in children had a good outcome in our patient.

## Predictors of prognosis at admission and 1st month in Guillain Barré syndrome

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*Objective.* Guillain-Barré syndrome (GBS) is an acute inflammatory immune-mediated polyradiculitis. Diagnosis of GBS is based on history and physical examination, supported by electrophysiological studies and cerebrospinal fluid (CSF) analysis. Despite affective treatments with plasma exchange (PE) and intravenous immunoglobulin (IVIG), mortality is 5% in GBS. In this study, we aimed to evaluate the predictors of GBS prognosis at admission and 1st month in our tertiary care institute. Methods. Electronic medical records of 166 GBS patients between January 2011 and October 2017 were analysed and only patients who had detailed physical examinations at admission and the first month and who had detailed clinical history, lumbar puncture (LP), electrophysiological and laboratory findings at hospitalization period were included for subsequent analysis. Hughes disability score (HDS), which is a well known disability scale ranging from 0 to 6 for GBS patients were evaluated at the end of first day and 1st month. Results. 81 patients were admitted to the study after considering exclusion criteria. The mean age was 52,2 ± 18.5. The mean HDS was 2.96 at admission and 1.94 at the end of 1st month. Age, plasma albumin levels and cerebrospinal fluid (CSF) protein levels were significantly correlated with low HDS scores. Age, plasma sodium, albumin, neutrophil/lymphocyte (NLR) levels, CRP and CSF protein levels were significantly correlated with the poor prognosis at the end of the 1st month. While concomitant cranial nerve palsies were correlated with low HDS scores, antecedent events (fever, respiratory infection, gastroenteritis) were not correlated. Conclusion. Analysis of prognostic predictors consistently demonstrates the negative impact of higher age, lower plasma sodium and albumin levels, higher CRP, NLR and CSF protein levels and the concomitant cranial nerve palsies. Further outcome studies may contribute to adequately integrate all potential factors in more reliable predictive models in future.

# Session 5. Duchenne muscular dystrophy and inflammatory myopathies

## Duchenne manifesting carriers with stop codon dystrophin gene mutations: to treat, or not to treat, that is the question

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Duchenne muscular dystrophy (DMD) is a X-linked degenerative disorder affecting skeletal muscles and myocardium due to mutations in the dystrophin gene, notably deletions, duplications and point-mutations. DMD female carriers are usually asymptomatic. However a few percentage of them may present symptoms at both skeletal muscle and cardiac level, that have been related to a skewed X-chromosome inactivation (XCI). Symptoms appear early, in the first decade of life, in girls with a XCI of the wild allele > 80%. A drug treatment for patients with DMD caused by stop codon gene mutations, still ambulant, has become recently available, based on the clear demonstration of its efficacy in slowing the course of the disease. The drug is able to read through the stop codons with the advantage of oral administration and better patient's compliance. As we retain it important, that symptomatic carriers with similar mutations should have the possibility to be treated too, in this report we present the preliminary results of Translarna administration in a still ambulant 24 year-old DMD manifesting carrier with a stop-codon in exon 53 (c.7792C > T; p.Gln2598Stop), who began the treatment in October 2017, at a dosage of 2,250 mg/die. At the pre-treatment examination the following parameters were evaluated: 6MWT (100 meters); NSAA (3/34); PUL (55/80). A subjective improvement of the strength was reported after two months. Unfortunately, at the beginning of December 2017, the patient had a traumatic fracture of the right femur that required surgical repair – not free from complications – and a prolonged rehabilitation. She discontinued taking the drug during this period and started taking it again on February 10th 2018. At the control of end of April, she was able to stand up and to walk unassisted indoor. NSAA and PUL were unchanged.

## Muscular dystrophy in a female patient with a homozygous nonsense mutation in DMD gene: case report

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*Objective.* Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are progressive muscular disorders caused by mutations in the dystrophin-encoding DMD gene located on Xp21. It is relatively frequent in male population with an incidence of 1/3,500 live male births whereas DMD is rare in female population with an incidence of 1 in 50,000,000 live female births. Two-thirds of mothers of affected males are thought to be DMD gene carriers and approximately 8% of female carriers has muscle weakness to some extent. We present here a female patient with a homozygous nonsense mutation in DMD gene. Methods. A 9-month-old girl, born to nonconsanguineous parents, is presented with weakness. Neurological examination revealed poor head control and axial hypotonicity. She could not sit without support. Deep tendon reflexes were hypoactive and no pathological reflexes were detected. Her aspartate aminotransferase (AST) and alanine amino transferase (ALT) levels were 138 U/L (10-37) and 134 U/L (10-40), respectively. Her creatine kinase (CK) level was 7,841 U/L (0-190). Her acid alpha glucosidase enzyme level for Pompe disease was normal. Her echocardiogram was normal. The genetic analysis for DMD with MLPA technique was normal. Her muscle biopsy was consistent with dystrophinopathy. She had a female karyotype, 46XX. Results. The diagnosis of DMD was made by sequencing of DMD gene. The patient is homozygous for c.1438G > T mutation in DMD gene resulting in a stop codon. Segregation analysis and UPD analysis are planned. Conclusions. Although rare in female population DMD should be considered in female patients with myopathy. Genetic analysis using MLPA technique is the first diagnostic tool, however, it only detects deletions and duplications, which constitute approximately 77% of all cases. Distrophin gene sequencing as a second step should be used to detect point mutations.

## Transient myocardial ischemia findings in Duchenne muscular dystrophy: case report

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*Introduction.* Cardiac dysfunction is frequently seen in patients with Duchenne muscular dystrophy (DMD) and can be a cause of death. Early diastolic dysfunction and focal fibrosis lead to cardiomyopathy. Cardiac involvement is frequently progressive and asymptomatic. In this report, a DMD patient presenting with transient ischemic findings was presented. *Case.* A 10 years old male patient diagnosed with DMD applied with chest pain while resting. Patient is transferred to our clinic because of his Troponin T level is found 50.00 mcg/l. Time from the beginning of his complaints until applying to our clinic was 9 hours. When the patient came to our clinic his complaints have regressed thoroughly. 4 mm ST elevation is detected at V4-V5-V6 and D2-D3-aVF. In patient's blood analysis, acute phase reactants were negative. Troponin T level was > 10ng/ml and CK-MB level was 958 mcg/l. Ejection fraction was 55-60% in patient's echocardiographic examination and it is noted there were no wall movements in the infero lateral segment of left ventricle which was compatible with ECG findings. Acute myocardial infarction was considered and the patient is taken into intensive care unit. Angiography was performed. In angiography it is observed that exit and anatomy of left and right coronary arteries were normal andthere were no lesions in favor of stenosis. Troponin T level regressed to 0.2 ng/ml in 6 days. ECG findings returned to normal in 5 days. It is observed that functions of inferolateral segment of left ventricle returned to almost normal which has no movement in echocardiography at first examination.

*Conclusions.* In this report, a patient applied with sympthomatic transient cardiomyopathic findings compatible with acut coronary syndrome is presented; in contradic-

tion to generally known asymptomatic and progressive cardiac involvment in DMD patients. Transient myocardial ischemia may be seen in DMD patients. This may be the first proof of cardiac involvement.

### Characteristics of motor, mental status and clinical course of our dystrophinopathies

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We conducted a descriptive, retrospective study including a total of 36 patients (83.3% DMD, 16.7% BMD) between 8-18 years of age. Mean age at evaluation was 133.6 (± 51.3) months old; only one patient was female and all patients had visited our clinic in the last year. Only 1 patient has autism, 17 patients (47.2%) needed special education due to learning disabilities (n = 4) and mental retardation (n = 13). In BMD group, all the patients were ambulatory. In DMD group ambulation were lost in 20 (55.5%) patients at a mean age of 9.5 years. 28 (77.8%) patients has genetic study include 1 exon skipping, 20 deletion, 3 duplication, 2 nonsense mutation, 2 non-stop codon mutation. In DMD population 27 patients (90%) were on steroids, 2 (5.5%) were never received steoids. In BMD population 3 (50%) were on steroids. One patient went on operation for his scoliosis. Long term and multidisiplinary follow-up is very important in dystrophinopathies.

### Meta-analysis of ataluren in patients with nonsense mutation Duchenne muscular dystrophy

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*Objective.* Ataluren is the first drug approved in the EU for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD). The aim of this meta-analysis was to evaluate the efficacy of ataluren in patients with nmDMD across a phase 2b (NCT00592553) and a phase 3 study (NCT01826487). Methods: Patients in the phase 2b study who met the phase 3 inclusion criteria were included in this analysis. Boys (7-16 years) with nmDMD, baseline 6-minute walk distance (6MWD) of ≥ 150 m and ≤ 80% of that predicted for their age and height, and ≥ 6 months of steroid use, received ataluren (orally, dosed 10, 10, 20 mg/kg/day) or placebo for 48 weeks. The primary endpoint was week 48 change from baseline in 6MWD. Week 48 changes in timed function tests (TFTs) were also assessed. The meta-analysis was repeated using all patients in the phase 2b study. Results: Overall, 291 patients were included in this analysis (phase 2b: ataluren, n = 32; placebo, n = 31; phase 3: ataluren, n = 114; placebo, n = 114). A benefit of 21.1 m in 6MWD (p = 0.0193) was observed in patients who received ataluren compared with placebo. Patients receiving ataluren also showed statistically significant improvements in time to run/walk 10 m (– 1.4 s; p = 0.0251), time to climb 4 stairs (– 1.6 s; p = 0.0184), and time to descend 4 stairs (– 2.0 s; p = 0.0044) versus placebo. Similar results were obtained when all patients were included (all endpoints, p < 0.05).

*Conclusions.* Patients who received ataluren over 48 weeks experienced a statistically significant clinical benefit, as measured by 6MWD and TFTs, compared with placebo.

### Slope analysis of 6-minute walk distance as an alternative method to determine treatment effect in trials in Duchenne muscular dystrophy

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*Objective.* Change in 6-minute walk distance (6MWD) from baseline to end-of-treatment is commonly used as a primary endpoint for Duchenne muscular dystrophy (DMD) trials. Once patients lose ambulation, they are assigned a 6MWD of 0 for the remaining visits. We compared this method with a slope analysis, whereby random intercepts and slope of change from baseline are fitted to change/week. We compared these two methods for assessing the efficacy of ataluren in patients with nonsense mutation (nm)DMD, including patients at high risk for loss of ambulation (LOA).

*Methods.* Change from baseline (using analysis of covariance [ANCOVA]) and slope analysis were performed on phase 3, 48-week trial data evaluating ataluren vs placebo in boys ≥ 7 - ≤ 16 years with nmDMD (Study 020/NCT01826487). 72-week data from the open-label extension (Study 020e/NCT02090959) were added. Slope analysis results were converted from change in metres/week to overall change from baseline following 48 or 72 weeks' treatment.

*Results.* Study 020: in the ITT population (ataluren, n = 114; placebo, n = 114), ANCOVA and slope analyses demonstrated similar benefits with ataluren over placebo in 48-week 6MWD (13.0 m vs 18.8 m, respectively). In patients with baseline 6MWD < 300 m, who experienced larger incidences of LOA, there was a greater ataluren benefit in 6MWD when estimated by slope analysis (– 7.7 m vs 61.1 m). Studies 020 + 020e: in Study 020e, all patients from Study 020 received ataluren; the slope separation observed between ITT patients who had previously received ataluren, vs placebo, was maintained at 72 weeks (difference = 21.9 m). The separation in patients with baseline 6MWD < 300 m widened from 48 to 72 weeks (ataluren vs placebo, difference = 80.2 m). Conclusion The slope analysis detected a considerable treatment benefit with ataluren vs placebo (particularly for patients with baseline 6MWD < 300 m), which was maintained for 72 weeks. This alternative methodology more accurately estimates a patient's rate of change in 6MWD than previously used methods.

## Long-term pulmonary function outcomes in non-ambulatory patients with nonsense mutation Duchenne muscular dystrophy treated with ataluren: 240-week data from an open-label extension study

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*Background.* Duchenne muscular dystrophy (DMD), an X-linked, recessive disease affecting ~ 1 in every 3,600-6,000 live male births, is caused by dystrophin gene mutations. Dystrophin is critical for myofiber structural stability and function; its absence leads to progressive muscle dysfunction, loss of ambulation, and early death from respiratory/cardiac failure. Forced vital capacity (FVC) < 1 L raises mortality risk in DMD patients. About 10-15% of patients have a dystrophin gene nonsense mutation (nonsense mutation DMD [nmDMD]), where a premature stop codon halts translation to generate truncated, nonfunctional dystrophin. Ataluren promotes ribosomal readthrough of the premature stop codon to produce a full-length dystrophin protein, treating the underlying cause of nmDMD.

*Objective.* To compare the effect of ataluren and standard of care (SOC) on lung function in non-ambulatory patients, and assess ataluren's safety and tolerability.

*Methods.* FVC data from non-ambulatory patients at study entry (unable to run/walk 10 m in ≤ 30 seconds) aged 9 to 18 years receiving oral ataluren (40 mg/kg/day [10, 10, and 20 mg/kg for morning, midday and evening doses, respectively]) were obtained from Study 019 (NCT01557400; begun in 2012; data cut-off Jan. 31, 2017), an international, multicenter, open-label trial that enrolled patients from previous ataluren PTC-sponsored trials at non-US study sites. Data for age-matched, non-ambulatory patients (wheelchair-bound) in subjects receiving SOC (not ataluren) were obtained from an ongoing natural history study (CINRG, NCT00468832; from 2012 through Nov. 18, 2016) and compared to 019 FVC < 1 L by Kaplan-Meier analysis.

*Results.* Subgroups included 38 ataluren- and 58 SOC-treated patients. At data cut-off fewer ataluren-treated vs SOC-treated patients had FVC < 1 L (7.9% vs 39.7%, respectively). FVC < 1 L was reached by 50% of SOC-treated patients by age) age 19.3 years (95% CI, 18.8-22.6). At age 19.3 years, only 16% of ataluren-treated patients had FVC < 1 L (p = 0.093). FVC < 1 L was reached by 50% of SOC-treated patientsafter 7.1 years (5.3-9.4) with SOC (log-rank test p = 0.067); 10% of ataluren-treated patients had FVC < 1 L after 4 years. Most adverse events (AEs) on ataluren were mild (29.5% of patients) or moderate (31.8% of patients). The most common AEs were nasopharyngitis (45.5%), headache (27.3%), vomiting (27.3%), and gastroenteritis (22.7%).

*Conclusions.* Findings suggest that ataluren preserves lung function in non-ambulatory patients with nmDMD. Safety and tolerability were consistent with previous findings.

## A phase 2 trial of the safety and pharmacokinetics of ataluren in patients aged ≥ 2 to < 5 years with nonsense mutation Duchenne muscular dystrophy

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Nonsense mutation Duchenne muscular dystrophy (nmDMD) is a rare, X-linked genetic disorder that results in a decline in function, loss of ambulation and early death due to respiratory or cardiac failure. Ataluren is conditionally approved by the European Medicines Agency for the treatment of ambulatory patients aged ≥ 5 years with nmDMD. Initiation of treatment prior to substantial muscle loss may maximize benefit. It is therefore important to understand the safety and pharmacokinetics (PK) of ataluren in patients aged < 5 years, particularly since ataluren is dosed by weight. A phase 2, open-label trial has been designed to evaluate the safety and PK of ataluren in boys aged ≥ 2 to < 5 years with nmDMD with a body weight ≥ 12 kg (NCT02819557). This trial will include a 4-week assessment of the safety and PK of ataluren, and a 48-week extension period to assess the safety of long-term administration of ataluren in this younger population. Motor function will also be evaluated. Fourteen patients were enrolled and are receiving ataluren 40 mg/kg/day (given orally in three doses: 10, 10 and 20 mg/kg) for 52 weeks. The primary endpoint will be the overall safety profile of ataluren with regards to the type, frequency, severity, timing and relationship to study therapy of any adverse events (AEs); occurrence of any dose-limiting toxicities; treatment discontinuation owing to AEs; and occurrence of serious AEs. Secondary endpoints will include assessment of plasma PK parameters on days 1 and 28 of ataluren treatment; changes from baseline to week 52 in timed function tests, North Star Ambulatory Assessment total score, body weight, height and body mass index; and ataluren palatability characteristics determined by a parent/caregiver questionnaire. Available data from this ongoing trial will be presented.

## Outcome of children with juvenile dermatomyositis: a tertiary center experience

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*Objective.* Juvenile dermatomyositis is an idiopathic immune inflammatory myositis that is rarely observed in childhood. While it is a disease characterized with proximal muscle weakness, heliotrope rash, and cutaneous findings such as Gottrons papules and calcinosis, it affects other internal organs such as lungs and heart. Corticosteroids and methotrexate are most effective medicines that have been used in its treatment for years.

*Method.* Fifteen patients who have applied to İnönü University Department of Pediatric Neurology and Rheumatology between years 2010-2017 and diagnosed with juvenile dermatomyositis (JDM) have been evaluated retrospectively.

*Results.* 80% of patients included in the study was female and 20% was male. Average age of patients was 9,26 ± 3,21 years. The period between complaints of patients and diagnosis was 7,8 ± 6 months in average. Average follow-up period after the diagnosis was 24,93 ± 15,28 months for our patients. 100% of our patients were observed to have muscle weakness, 93,3% had Gottrons papules, and 80% had heliotrope rash. 66,6% of

patients underwent muscle biopsy, 60% of patients underwent EMG, and 33,3% of patients underwent muscle MRI. Corticosteroids and immunosuppressive agents were administered to our patients in their treatment.

*Conclusions.* Juvenile dermatomyositis is an inflammatory myositis that is rarely observed in childhood. Good response may be obtained with early diagnosis, intense immunosuppressive treatment and effective physical therapy.

### Early diagnosis of juvenile dermatomyositis in a child: the importance of MHC-1 overexpression on sarcolemma

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*Introduction.* Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy of childhood, characterized by pathognomonic skin rashes and proximal muscle weakness. Although mortality and morbidity of JDM have significantly improved with the advent of immunosuppressive therapies, delays in diagnosis can result in a chronic disease course, severe morbidity and even mortality.

*Case.* A 8-year-old girl was admitted to our clinic with the complaint of muscle weakness of lower limbs and myalgia for two weeks. She had an upper respiratory tract infection about two months ago, and muscle weakness has first appeared one month after the infection, then increased in the last two weeks. On physical examination, she had ill-defined pale violescent rash around eyelids herald the heliotrope rash, red papules over the skin of the metacarpophalangeal and distal interphalangeal joints suggestive of Gottron papules and also hyperemic rash on elbows and knees. There was slight proximal muscle weakness on lower limbs and has increased on follow-up. Hoarseness and dysphagia with solid foods were started 2 weeks after the admittance. Serum creatine phosphokinase(CK) level was found 8400 U/L (0-145 U/L). Viral serology tests and connective tissue disease-associated antibodies were negative. Muscle biopsy revealed MHC-1 antigen overexpression on sarcolemma but no infiltration or perifascicular atrophy. She was diagnosed with JDM and started on prednisone, methotrexate and hydroxychloroquine treatments. Proximal muscle weakness, hoarseness and dysphagia disappeared two weeks after the initiation of treatment, along with the decrease of serum CK levels to normal range.

*Conclusions.* Early diagnosis and treatment is crucial for the prognosis of JDM and known to be related with favorable outcome. MHC-1 antigen overexpression on sarcolemma in muscle biopsy is an early finding of JDM, even in absence of inflammation and cellular damage, and it is a useful marker for early diagnosis of the disease.

### Juvenile myositis presenting with angioedema

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*Introduction.* Juvenile dermatomyositis is the most common inflammatory muscle disease in childhood. Besides the typical skin findings in juvenile dermatomyositis, angioedema and capillary leak syndrome were also rarely reported in the literature.

*Material and methods.* Two-year-old girl was reported to the hospital with acute walking disability, generalized skin edema, swelling of lips and muscle ache. Skin and mucosa findings were defined as angioedema. Muscle enzyme levels and erythrocyte sedimentation rate were increased, but serum albumine and sodium levels were normal, inappropriate for capillary leak syndrome. C1 esterase inhibitor level was found normal. Muscle magnetic resonance imaging of lower extremities showed generalized T2-weighted signal increase compatible with inflammation. Inlammatory muscle disease was diagnosed with clinical and laboratory findings. Because of the absence of typical skin findings for juvenile dermatomyositis, skin biopsy was done and prednisolon was ordered.

*Results.* Clinical findings were improved in a short period after prednisolon treatment and serum CK level decreased to normal limits. At the third week of treatment, the patient started to walk independently. Perifascicular atrophy could not be shown at muscle biopsy, but MHC-1 expression was mildly increased. The patient was diagnosed as juvenile myositis, and it is planned to observe skin involvement for juvenile dermatomyositis in the follow-up.

*Conclusions.* It is suggested to define that patients who have clinical and laboratory findings of muscle inflammation without typical skin involvement as juvenile myositis, but angioedema, the presenting skin finding in our patient, may be one of the skin finding of juvenile dermatomyositis.

## Session 6. Myopathies

### Diagnostic yield of muscle biopsy in infants: retrospective analysis of clinical and histopathological findings

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*Objective.* Diagnostic work up of infants with neuromuscular involvement includes multidisciplinary approach comprising of metabolic, radiologic and molecular genetic analyses after a through history and physical examination. However non-invasive laboratory tests may not be informative and muscle biopsy may facilitate diagnosis and/or guide further diagnostic studies in congenital myopathies, congenital muscular dystrophies, metabolic and mitochondrial myopathies. We aimed to define the clinical and histopathological findings of infants who underwent muscle biopsy and identify the diagnostic yield of muscle biopsy in this cohort.

*Methods.* All 0 to 2-year-old children who underwent mus-

cle biopsy from 01.01.2010 to 31.03.2017 in Ankara Childrens Hematology-Oncology Training and Research Hospital, were included in the study. Muscle biopsies were evaluated in Hacettepe University Children's Hospital, Pediatric Pathology Unit. Patients' demographic information, clinical findings, creatine kinase (CK) levels, histopathological findings and clinical-pathological correlation were investigated.

*Results.* Eighty-seven patients were included in the study. Sixty-four (73.6%) were male, 23 (26.4%) female (M/F = 2.8). Mean age was 9.73 ± 7.04 m. Developmental delay and hypotonia were the most frequent clinical findings (64.4% and 59.8% respectively) and mitochondrial disease was the most frequent clinical diagnosis (61%), followed by muscular dystrophy (15.9%) and congenital myopathy (11.5%). CK level was normal in 65.9%, while 17.1% had CK > 1,000 U/L. Specific pathological findings were identified in 38 biopsies (43.7%). Most frequent pathological features were findings compatible with mitochondrial/metabolic myopathy (14 patients, 16.1%) and muscular dystrophy (12 patients, 13.8%). Myopathic changes were present in 7 biopsies (8.0%) and neurogenic changes in 5 (5.7%). Clinical diagnosis was compatible with pathologic diagnosis in 24 patients (63.2%).

*Conclusions.* Diagnostic yield of muscle biopsy remains significant. Especially in this age group, with mitochondrial disease being a major diagnostic challenge, muscle biopsy helps to support clinical diagnosis and guide further studies.

## Genotype-phenotype correlations in novel form of PYROXD1-related congenital myopathy

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Recently mutations in the gene PYROXD1 (pyridine nucleotide-disulphide oxidoreductase domain 1) were shown in nine patients of five families to cause early onset myopathy with internalized nuclei and myofibrillar disorganization Here we present two unrelated cases with mutations in PYROXD1. The first case is a 15-year-old female patient from a consanguineous family with three affected children. She walked at 12 months of age, but presented at six years of age with generalized weakness more proximal than distal, including facial weakness and swallowing difficulties. A muscle biopsy showed cores in the muscle fibers and a type 2 myofibers atrophy. An affected sibling, an older brother, died of cardiomyopathy at 14 years of age, the other affected sibling had severe weakness at 38 years of age and can still walk with support.. Whole exome sequencing (WES) revealed a co-segregating homozygous missense variant in PYROXD1 (NM_024854, c.464A > G, p.N155S) in the two surviving children. The second case is a male patient, only child of consanguineous parents (cousins) from Turkey, who was diagnosed with congenital myopathy with normal CK levels. Muscle biopsy showed dystrophic changes, a moderate increase of interstitial connective tissue, high amount of fat and type 2 myofibre atrophy. We were unable to identify the causative mutation for this patient using Mendeliome sequencing (Illumina TruSight one, v1, 4813 genes). WES lead to the identification of two variants in PYROXD1, the Turkish founder mutation (c.464A > G, p.N155S) and a novel frameshift variant (c.329_332delTCTG, p.L112Vfs*8). Sanger sequencing of the parents confirmed the compound heterozygosity of the mutations. The here presented patients show an overlapping PYROXD1 phenotype, with mild limb girdle weakness, slow progress, nasal speech, facial weakness and normal to high CK-levels. The phenotype of the PYROXD1 patients is similar to patients with centronuclear myopathy without ophthalmoplegia. This second report strengthens the association of recessive mutations in PYROXD1 and early-onset myopathy with internalized nuclei. We expand the phenotype to childhood death due to cardiomyopathy.

## Distal myopathies: genotype-phenotype relationships of six patients

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*Aim.* Distal myopathies are a group of rare muscular dystrophies which predominantly effect feet and hands. The clinical findings of different distal myopathies may overlap. The aim of this study was to analyze the clinical and molecular genetic analysis of 6 distal myopathy patients who admitted to our neuromuscular clinic within the last two years.

*Methods.* We investigated 6 index patients in point of semiologic features, neurological examination, electrophysiology, muscle biopsy, and molecular genetic analysis. There were 3 men and 3 women. The mean age at onset was 23.2 years. Although consanguinity was reported in 2 patients, 3 patients' parents were from the same village. All of the patients had symmetric calf atrophy. One patient with LGMD type 2B had kyphoscoliosis. Five of the patients had distal or predominantly distal weakness in lower extremities. Three patients had proximal weakness in addition to distal weakness. Neurological examination was normal in one patient with LGMD type 2B. CK levels were more than 3-fold high except one dysferlinopathy patient with normal CK levels. Muscle biopsy revealed myopathic changes in all patients. Molecular genetic testing showed a rare compound homozygous mutation in anoctamin 5 gene in one patient, homozygous c.5668-7G > A mutation in LGMD type 2B in one patient and heterozygous mutation in c.1966A > G, c.2539C > T and c.2338C > T in DYSF in three patients with LGMD type 2B. The remaining one patient had ColQ mutation.

*Conclusions.* Our findings indicated a clinical spectrum for distal myopathies might overlap but they are usually underrecognized diseases by neurologists.

## Titin and titinopathies: the state of the art

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Titin (TTN) gene contains 363 coding exons and encodes a sarcomeric protein spanning from the Z-disk to the M-band. TTN mutations cause a wide spectrum of genetic disorders, including several skeletal muscle diseases characterized by a different age

of onset, progression and muscle involvement. High throughput sequencing strategies have been revealing an increasing number of private and ultra-rare variants in the TTN gene, widening the spectrum of TTN-related diseases. At the same time, the interpretation of these variants of uncertain significance is a critical issue for clinicians and researchers. TTN variants in inherited myopathies challenges the previously established ACMG/AMP guidelines for disease-associated variants. Predictive bioinformatic tools are unable to correctly predict the effect of most missense TTN variants and the information deduced from the current databases is often ambiguous so that their use is misleading in the clinical context. In a collaborative effort aiming to improve the interpretation of TTN variants, a TTN specific database shared between the research groups and integrated with the RD-Connect system has been created. The increased number of causative variants and patients identified has partly allowed a dissection of the genotype-phenotype correlation. A prenatal or congenital phenotype with a stable postnatal disease-course or weakness amelioration, for example, arises from mutations in specific exons only expressed in a prenatal stage. Further studies about TTN expression in different tissues (heart and different skeletal muscles) and/or different physiological and pathological states would deepen our understanding of the role of TTN variants in complex human diseases. A better understanding of the molecular basis of titinopathies is a mandatory first step towards possible therapeutic approaches.

## FHL1 gene related X-linked reducing myopathy type 1a mimicking polyglucosan myopathy histopathology

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*Introduction.* FHL1 gene mutations are responsible for Uruguay fasciocardiomusculoskeletal syndrome, Emery-Dreifuss muscular dystrophy type 6, X-linked myopathy with postural muscle atrophy, X-linked reducing body myopathy type 1a and 1b, X-linked dominant scapuloperoneal myopathy. Here, we present a 5-year-old girl with X-linked reducing body myopathy type 1a (severe infantile or early childhood onset) whom muscle biopsy findings were reported as polyglucosan myopathy.

*Material and methods.* A-five-year old girl was reported for walking disability at two years of age. She had prominent muscle wasting of upper and lower extremities proximal muscles and neck flexors. Deep tendon reflexes were absent. Her cognition and the rest of the physical examination were normal. Her serum CK level was moderately incresaed. At follow-up her muscle wasting became worse, and she became bedridden with requirement of continuous positive mechanical ventilation.

*Results.* Muscle biopsy was interpreted as polyglucosan myopathy. Genetic analysis for glycogen storage disease type 4 and polyglucocan myopathies were found normal. Targeted next genetaion sequencing analysis for muscular disorders revelaed FHL1 mutation.

*Conclusions.* X-linked reducing myopathy type 1a is a severe, rapidly progressive myopathy, leading to proximal muscle weakness and atrophy, loss of ambulation, contractures, and often respiratory insufficiency. Muscle biopsies of these patients show FHL1-positive aggregates and reducing bodies, and should be differentiated from polyglucosan myopathies which show amylopectin-like deposits reminiscent of a glycogen storage disease.

## Neuropathy? Myopathy? Nemaline myopathy type 2 case

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Nine years old male patient was admitted for difficulty in walking. Personal history revealed that the patient had slipped from gynecologists hands in birth and had bilateral femoral fracture, he was hospitalized in a neonatal unit. The family was informed that a femoral subluxation was formed in both hip joints after the casts were removed because of the casting. After bandaging prosedüre a total subluxation was seen in hips and he was operated at age of four months in a university hospital, he had four revised operations afterwards. After intense physiotherapy he succeeded walking independently at the age of 3 years old. He was referred to several hospitals for his waddling gate, Electromyography studies showed (first EMG at five years old) chronic neurogenic findings, proximal prominent 2nd motor changes, (2nd EMG at 7 years old ) L3-4 at right and L3 and S1 radicular difficulty at left, (3rd EMG in 2016) Chronic neurogenic difficulty was stated. His parents were first degree cousins, The patient had a waddling gate, deep tendon reflexes were reduced, proximal muscle weakness was present in his physical examination. His laboratory values showed creatinine kinase: 202 U/l, Spinal magnetic resonance imaging showed slight dorsal kyphosis, genetic examination for spinal muscular atrophy were normal. Tru sight inherited disease sequencing panel showed heterozygous nonsense mutation in NEB gene c.10882 A > C, c.4030G > A, c.21627 T > C and c.8499G > A.This change was stated to be responsible for it was nonsense. Nemaline myopathy 2 is inherited in autosomal recessive pattern, myopathic facial muscles and neck weakness is characteristic, skeletal muscle deformities and scoliosis is present, hypotoni in newborn is remarkable. Muscle weakness is proximal, distal weakness develope in later years. EMG findings reveal myopathic initially, neuropathic changes are seen later. Muscle biopsy of the patient is under study. This patient is presented for the discussion of the syndrome.

## Evaluation of the characteristics of critical illness myopathy patients

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*Objective.* Critical illness myopathy (CIM) is an important cause of weakness in intensive care unit (ICU) patients, giving rise to difficulty in weaning from mechanical ventilation and disability after discharge. Diagnosis is primarily based on clinical findings, while electrophysiological investigation and biopsy assist in determination of the pathological process. We aimed to share the clinical features of our patients with CIM who were followed up in our clinic.

*Method.* Between June 2017 and April 2018, 32 patients who were referred to our clinic and who received a CIM diagnosis were evaluated. Socio-demographic characteristics of patients (age, sex) EMG results, keratin phosphokinase values, intensive care first-time admission, duration of ICU and prognosis were recorded. Furthermore during follow-up in ICU, sepsis,

multiple organ failure, hyperglycemia use of corticosteroids or neuromuscular blocking agents were recorded.

*Results.* Twenty-two of the patients were male and 10 were female. The mean age was 53.6 (min 23, max 82). Nine patients had anormal keratin phosphokinase levels. In all patients, needle EMG showed early interference and low amplitude polyphase myogenic MUP and MUP loss in proximal muscles. Patients had ICU, 19 of them with asthma, 7 with stroke 3 with trauma and 3 with intoxication. There were 28 cases of sepsis, 4 cases of multiple organ failure and 24 cases of hyperglycemia during ICU admission. When using corticosteroids in 25 patients no neuromuscular blocking agents were used in any of the patients. The mean duration of ICU was 22 days (min 9, max 80). Twelve patients were completely recovered on follow-up and 11 patients were partially recovered. 9 patients died in ICU.

*Conclusions.* The incidence of CIM may be reduced by eliminating the currently defined risk factors. Although specific therapies have not been discovered, supportive treatment, aggressive management of sepsis and elimination of contributory medications may be beneficial.

## Session 7. General topics

### Anesthetic management of a child with dermatomyositis

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*Objective.* Dermatomyositis is a rare diseaes characterized by proximal muscle weakness due to the inflammation and degeneration of muscles. In this case we present an anesthetic management in a patient diagnosed as dermatomyositis. (1)

*Case presentation.* A five year old boy, diagnosed a case of dermatomyositis was scheduled for upper endoscopy for dysphagia. He had weakness bilateral, had rash on both arms and on forehead.

Respiratory, cardivascular, abdominal systems revealed normal. His treatment consisted of prednisone. Sedation was planned. After preoperative stabilisation and written informed consent from the parents, he was premedicated with prednisone and an hour later taken to the operating room.

In the operating room, the routine monitors were attached and intravenous (IV) access established with a 24 G cannula. Sedation was accomplished with propofol intravenous (i.v.) 0.5 mg/kg maintained with a propofol infusion and 0.5 µg/kg/min remifentanil i.v. infusion. He received nasal oxygen breathing spontaneously. Oxygen saturation was maintained between 97% and 100%. Body temperature, heart rate, noninvasive blood pressure, $O^2$ saturation, and end-tidal $CO_2$ were stable during the procedure and postoperative period. The ETCO2 was checked by a capnograph. We did not use train of four stimulation as we didn't use neuromusculer agent.

*Conclusions.* The anesthetic problems encountered in patients with dermatomyositis undergoing general anesthesia may have respiratory, cardiovascular, haemopoietic problems. Airway protection and ventilation are the two main concerns. Swallowing and vocal cord dysfunction may lead to aspiration into the trachea. Patients can have a diminished cough reflex due to the weakness of thoracic muscles. Postoperative pain relief should be planned with a titrated analgesic regime Our patient had an uneventful recovery at all occasions.

### Anaesthetic management in mucopolysaccharidosis

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Mucopolysaccharidosis (MPS) represents a group of rare lysosomal storage disorders associated with high prevalence of airway obstruction and restrictive pulmonary disease in combination with cardiovascular manifestations. These patients may have undergone to various operations for reconstruction. The anaesthetic problems include airway obstruction, difficult ventilation and/or intubation, possible emergency tracheostomy as well as cardiovascular and cervical spine anomalities. Because of the high anaesthetic risk, the benefits of a procedure in patients with mucopolisaccaroidosis should always be balanced against the associated risks. Therefore, careful evaluation of anesthetic risk factors should be done before the operation; including evaluation of airways,respiratory and cardiac functions and cervical spine. In this manuscript we presented anesthetic management of the three child with mucopolysaccaroidosis type IV (Morquio syndrome) undergoing various neurosurgical procedures.

### Early presentations of Schwartz-Jampel syndrome: that is all in the clinical phenotype!

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*Introduction.* Schwartz-Jampel syndrome (SJS) is a rare autosomal recessive disorder characterized by myotonia and skeletal dysplasia, caused by mutations in heparan sulfate proteoglycan (HSPG2) gene, encoding perlecan. Diagnosis is based on clinical and electrophysiological findings.

*Case 1.* A forty-day-old baby presented to our clinic with arthrogryposis and feeding difficulty. Intrauterine movements were normal. Pregnancy and birth was uneventful. She was born at 39. gestational week with a birth-weight of 2,250 gr. Parents were first cousins. Physical examination revealed short neck, low-set ears, high-arched palate, pursed lips, puckered chin. She had bilateral blepharospasm which was more prominent when she cries. There were mild muscle stiffness and flexion contractures on both hands and elbows. Diagnosis on clinical grounds was supported by electromyography demonstrating pseudomyotonic discharges.

*Case 2.* A 2-year-old girl was referred to our clinic with muscle stiffness and facial dysmorphism. She was born at 29th gestational week with a birth-weight of 1,540 gr. Her developmental milestones were normal. There was no consanguinity. She had a short stature (68 cm (< 3p), 9.5 kg (3p)), short neck and distinctive facial features including low-set ears, narrow palpebral fissures, bilateral ptosis and blepharospasm, pursed lips, puckered chin. Bone radiography showed shortening and bowing of long bones. Electromyography showed myotonia-like discharges. Diagnosis was further confirmed by identification of a compound heterozygous mutation in HSPG2.

*Conclusions.* Diagnosis of SJS depends on recognition of the clinical and electrophysiological phenotypes. Muscle stiff-

ness, skeletal deformities and characteristic facial features are clues, and SJS should be included in the differential diagnosis of not only myotonias in childhood, but also arthrogryposis in the newborn period.

### A rare familial tremor: hereditary geniospasm

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*Introduction.* Neuromuscular disorders often involve and may present with facial symptoms. This may lead to unnecessary neuromuscular work-up for rare movement disorders.

*Case.* The patient is an infant boy referred for atypical movements. He has involuntary, intermittent trembling of the chin during day time (video). It may be ceased by speaking, eating or distraction. Trembling is provoked by crying, agitation and focusing. There are not any other atypical movements. Developmental milestones were achieved properly. His physical and neurological examination is normal. Parents reported that the father, the paternal grandfather and uncles also had the same condition. The father only has trembling in case of psychological or physical stress. The family observed that chin trembling resolved with age.

*Discussion.* This boy (and the other members of the family) suffer from hereditary geniospasm (MIM 190100). It is a rare autosomal dominant condition caused by continuous or intermittent tremulous activity of the mentalis muscle. Trembling is characterized by paroxysmal, rhythmic, up-and-down movements of the chin and/or lower-lip. Although it is a benign condition decreasing with age, some patients may suffer from difficulties in social life. In selected cases, benzodiazepines, haloperidol, phenytoin and botulinum toxin were found to be effective.

*Conclusions.* Recognizing this sign would help prevent irrelevant examinations and concerns

### A rare cause of hypotonia: congenital myotonic dystrophy type 1

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Hypotonia is decrease in muscle tone due to various causes. In this case report, to draw attention to this rare disease a case which congenital myotonic dystrophy type 1 (CDM 1) diagnosis by clinical findings and hypotonia was presented.

*Case.* A 6 month old male case was admitted due to weakness. On the physical examination of the patient, it was seen that there was hypotony in the Landau test and head traction test. Metopic suture closed. DTR ++/++. CK: 69 u/L. ECG and cardiac evaluation are normal. There were similar findings in a sister who lives for forty days. There is once a story of vomiting with stool. Followed by a stigma in both lower and upper GIS in contrasted radiographs. Brain MR is include bilateral chronic subdural effusion, ventricular mild broadening, mild broad appearance at peripheral CSF distances, trigonocephaly due to metopic sinusoides. Electrophysiologic evaluation revealed normal motor and sensory nerve conduction studies in both upper extremity. However deep peroneal motor nerve responses were absent by stimulating at ankle and head of fibula. Needle EMG revealed neither spontaneus nor voluntary activity in extansor digitorum brevis muscle in contrast normal motor unit potentials at tibialis anterior muscle. Additionally 5 Hz and 10 Hz repetitive stimulation exhibited normal values. On the other hand there was no myotonic discharges in both proximal and distal muscles and muscle cooling had no effect on needle EMG findings. We did not able to perform exercise tests. Frontal baldness and myotonia findings were detected in his mother. Also needle EMG examination of her revealed myotonic discarge. With present clinical symptoms, CDM 1 was diagnosed in the patient. Genetic testing was recommended to the family and the patient was followed up.

*Result.* If there is a family history in cases with hypotonia, CDM 1 should be considered in the differential diagnosis.

### Co-existence of polyneuropathy, osteoporosis and limb-girdle muscular dystrophy in a patient with ankylosing spondylitis

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Limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of autosomal recessive and dominant disorders characterized by progressive weakness of shoulder and pelvic-girdle muscles. Ankylosing spondylitis (AS) is a chronic, systemic, autoimmune and inflammatory rheumatic disease, which primarily affects the vertebral and sacroiliac joints of the body. Peripheral neuropathy is one of the most common complications of diabetes mellitus that micro inflammatory changes have also been proposed in the highly complex disease pathogenesis. Painful paresthesia in distal limbs and symptoms due to the involvement of autonomic nervous system are frequently seen in those patients. Osteoporosis is a skeletal disorder characterized with decreased bone mineral density and disruption in structural integrity of bones that increases the risk of fractures, significantly. Ageing has been defined as an important risk factor for osteoporosis; however, immobilization, inflammatory rheumatic disorders and various endocrine diseases might also precipitate osteoporosis by decreasing the load on the bones. We hereby report a case of a patient diagnosed with a genetic neuromuscular disease and multiple autoimmune diseases (namely, AS and DM) and discuss the possible pathogenesis in line with the literature.

*Case report.* A 46-year-old man was admitted with the complaint of painful and swollen ankles, stiffness in neck and limb joints, and paresthesia in distal limbs. He was diagnosed with limb-girdle muscular dystrophy 20 years ago, with the symptoms of slowly progressive weakness in proximal limb muscles, which started during his early twenties, increased levels of serum creatinine kinase (CK), myopathic changes in electromyography and dystrophic changes in muscle biopsy. He was diagnosed with type 2 Diabetes Mellitus (T2DM) 10 years ago. His daughter was diagnosed with ankylosing spondylitis and was using non-steroid anti-inflammatory medications, besides regular physiotherapy. Ten years ago, he was operated due to right femur fracture after a fall and was unable to walk after a one-year period of postoperative immobilization. He was using a wheel chair and his functional activity level was 0. Examination revealed severe atrophy in shoulder and pelvic-girdle muscles. Cervical mobility was painful and restricted in all directions. Dorsal kyphosis was increased. There were flexion

contractures in both hip joints and right knee. Bilateral sacroiliac joints were painful with palpation. Lumbar motility could not be evaluated. Right ankle was swollen and warm with arthralgia. Muscle strength was 2/5 in proximal and 3/5 in distal muscles in upper limbs, and 2/5 in both the lower limbs. He had distal symmetric hypoesthesia in stocking and glove distribution. He was severely dependent with Barthel index score as 25. Serum and urine biochemical tests were within normal limits except erythrocyte sedimentation rate (53 mm/h), serum C-reactive protein (1.97 U/dL), creatinin kinase (459 U/dL), and lactic dehydrogenase (601 U/dL). HLA-B 27 was positive. Sacroiliac joint magnetic resonance imaging (MRI) revealed bilateral ankylosis. There was edema in right ankle and epin formation in right calcaneus and syndesmosis in C3-4-5-6 cervical vertebral corpuses in direct X-ray graphy. Total Z-score in hip was – 2.6 in bone mineral density. Distal symmetrical sensory polyneuropathy was detected in electrodiagnostic studies. He was treated with indomethacine 75 mg/d, salazopyrin 2000 mg/d, pregabaline 150 mg/d and dalendronate 70 mg/w with cholecalciferol 2800 IU/w. He was enrolled in a personalized physiotherapy program. CRP level and sedimentation rate were decreased 3 months later. Total Z-score in hips was increased to – 1.6 one year later.

## 1p36 deletion syndrome with a Pompe disease-like presentation

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*Objectives.* Monosomy 1p36 is considered to be the most common subtelomeric microdeletion syndrome, one that occurs in approximately one in 5,000 live births. The syndrome is characterized by developmental delay, growth impairment, generalized hypotonia, heart defects, hearing impairment and cognitive delay.

*Case presentation.* A two-year-old girl presented with generalized hypotonia, failure to thrive and feeding difficulties. Her maximal motor capacity was the ability to sit without help. She had deep-set eyes, a long philtrum, and a pointed chin. Deep tendon reflexes were hypoactive. She was unable to speak meaningful words. Hearing tests were normal. Laboratory examination revealed a high level of creatine kinase, at 421 u/L. Echocardiography was suggestive of cardiomyopathy.

*Results.* Enzyme analysis for acid alpha-glucosidase was negative. Chromosomal microarray analysis revealed 2.3 Mb de novo deletion at 1p36.3 region.

*Conclusions.* 1p36 deletion syndrome is important in the differential diagnosis of generalized hypotonia and cardiac defect mimicking Pompe disease. Young children may pose a particular diagnostic challenge.

## Cohen syndrome: a case report

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*Background.* Cohen syndrome is a rare disorder with a broad spectrum of phenotypes. Mental retardation, ophthalmological anomalies, microcephaly, obesity, clumsiness and muscle weakness are the most common findings.

*Case presentation.* A 12-year-old male presented with muscle weakness. At neurological assessment, widespread hypotonia, joint hypermobility and dysmorphic facial features as thick hair eye brows and lashes were noted. Ophthalmological evaluation pigmentary retinopathy The hands were small with tapering fingers. He also presented truncal obesity. Communication and social skills were impaired. He had intellectual disability with autistic-like traits. He was referred to our hospital with myopathy prediagnose for muscle biopsy. He was diagnosed as Cohen syndrome, no muscle biopsy was performed.

*Conclusions.* Cohen syndrome is a rare disease causing widespread weakness and should be kept in mind in children with dysmorphic features and ophthalmological problems.

## Non-traumatic myositis ossificans in a four-year-old girl

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*Introduction.* Myositis Ossificans (MO) is a non-neoplastic heterotopic form of ossificiation in which bone tissue occurs in muscles and soft tissues. Both traumatic or non-traumatic causes can lead to this disease, which may be seen at any age with a predilection in adolescents and adults. We want to report a case of a four-year-old girl who developed non- traumatic MO within multiple muscles.

*Case.* A four-year-old girl was referred to our department with painful multiple muscle stiffness which were not secondary to trauma. On physcial examination well-circumscribed stiffness were palpated at following locations: on the anterior surface of the right upper arm between shoulder and elbow, on the back with extension between right paraspinal muscles and posterior superior iliac spine and on the right lateral aspect of the neck. The muscle areas were painful, smooth and were not warm to the touch. She had no rashes. She had not muscle weakness but her neck and right extremity movements were limited due to muscle stiffness. Basic biochemistry and rheumatological parameters were in normal range. No significant calcification was observed on radiography. Increase of echogenicity with edema and heterogenity with linear echogenities suggestive of calcifications of sternocleidomastoid muscle, biceps, erector spina and rectus abdominis muscles was detected on ultrasound imaging. Cervical-thoracic-sacral spinal MRI revealed thickening and hyperintensity of muscles and subcutaneous tissue.

*Discussion.* Myositis Ossificans is a very rare clinical entity. There is no sufficient information about genetics. Biopsy can lead to misdiagnosis as sarcoma, as well as, owing to its traumatic effect, to an exacerbation of the disease. Therefore, MO is considered a "don't touch lesion". However, radiologic findings and clinical follow-up may be helpful in establishing the diagnosis. Myositis Ossificans has no effective treatment, thus the prognosis may be poor, particularly in non-traumatic cases.

# Session 8. General topics

## Ataluren and physiotherapy in a boy with nonsense mutation Duchenne muscular dystrophy: 2 years' follow up case report

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*Objectives.* To evaluate effects of combined of ataluren and physiotherapy on functional performance, endurance, ambulation and fatigue in boy with DMD 2 years follow up.

*Method.* The boy with DMD was 12 years old. Timed performance tests (TPT), North Star Ambulation Assessment (NSAA) and 6MWT are used to evaluate functional performance and ambulation. Timed up and go test (TUG), 1 minute sit and stand test, 30 second calf raise test and VAS developed for children was applied to evaluate balance, endurance, fatigue, respectively. Exercises were done 3 days in a week for 96 week supervised by physiotherapist. Ataluren was taken three times a day and the recommended dose is 40 mg/kg (making a total daily dose). Evaluation parameters were repeated at 12 week intervals for 96 weeks.

*Results.* After ataluren and physiotherapy, TPT were shorter, NSAA score rose from 22 to 28 and 6MWT distance increased from 390 to 525. TUG test increased from 8.11 to 5.93 and 1 minute sit and stand test increased from 20 to 25. Thirty second calf raise test improved from 20 to 36. VAS score were decreased from 3 to 0.

*Conclusions.* Improvements in performance, endurance and ambulation after ataluren and physiotherapy show us that combined of ataluren and physical therapy may be proper treatment in DMD in long term. We think that there is a need to prospective follow up studies in large sample size.

## The association of scoliosis, pain and respiratory functions in DMD patients

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*Aim.* The aim of this study was to evaluate scoliosis, pain and respiratory functions in patients with Duchenne muscular dystrophy (DMD).

*Material and methods.* A retrospective cross sectional study was conducted in neuromuscular diseases Unit of Izmir Tepecik Training and Research Hospital. 61 patients diagnosed with DMD by clinical, laboratory findings and molecular analysis were included in the study. The clinical data containing demographic variables, baseline scoliosis radiographs and pulmonary function tests were recorded from the files of patients. Musculoskeletal pain symptoms which were questionned before were evaluated.

*Results.* A total of 61 male patients were included in this study. There were 32 patients with scoliosis in DMD patients. The mean age was 11,26 ± 5,46. The percentage of patients with scoliosis who had mild to moderate respiratory impairment was 25% and who had severe respiratory impairment was 34%. A statistically significant association was found between the presence of scoliosis and respiratory dysfunction. 23 patients with scoliosis and 3 patients without scoliosis had pain. A statistically significant association was found was found between scoliosis and pain ($p = 0.000$).

*Conclusions.* The results of our study suggest that a statistically significant association was found between scoliosis and respiratory dysfunction and between scoliosis and pain.

## Investigation of factors affecting hand functions in nonambulatory patients with Duchenne muscular dystrophy

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*Objective.* This study was planned to determine the factors affecting hand function of children with Duchenne muscular dystrophy who have lost walking ability and to investigate the effects of these factors on general upper extremity performance and quality of life.

*Method.* Twenty-three patients from Level 1-5 according to Brooke Upper Extremity Functional Classification (BUEFC) were included in our study. Age, duration of wheelchair usage, and steroid usage of children were recorded. Performance of upper limb, hand functions, passive range of motion limitations, thumb opposition, tripod, lateral, two-point pinch strengths, gross grip strength, all upper extremity muscle strength including shoulder, elbow, hand and wrist, and the quality of life of children and their parents were assessed. Results: It was determined that BUEFC, duration of wheelchair use, all grip strengths, shoulder abductor, horizontal adductor and elbow flexor muscle strengths and total upper extremity muscle strength were the factors that affect hand functions ($p < 0.05$). In addition, all the factors affecting hand functions were related to general upper extremity performance ($p < 0.05$). From these factors, BUEFC and shoulder horizontal adductor muscle strength were found to be correlated with PedsQL-child, and BUEFC and duration of wheelchair use were found to be correlated with PedsQL-parent ($p < 0.05$). No limitation was found in thumb opposition and range of motions. Conclusion: As a result, it was determined that even if they have full thumb opposition and range of motions, their manual dexterity are affected from muscle weakness more than range of motion and thumb opposition. Besides, distal functional abilities were found to effect quality of life of both children and parents.

## Investigation of the relationship between gait parameters and fear of falling in children with Duchenne muscular dystrophy: a pilot study

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*Objective.* The aim of this study was to investigate the relationship between spatio-temporal parameters of gait and fear of falling (FOF) in children with Duchenne muscular dystrophy (DMD).

*Method.* Sixteen children with DMD whose ages were between 6-15 and functional levels were between 1-4 according to Brooke Lower Extremity Functional Classification were included in the study. The demographics were recorded. FOF was as-

sessed by using ICF Based Fear of Falling Assessment in pediatric neuromuscular diseases (IBFOF) which was developed by researchers of this study. IBFOF consists of six titles which were based on ICF headings and the total score ranges between 0-68. Spatio-temporal characteristics of gait including walking speed (meter per minute), step length, stride length, step width, and stance width (measured by footprint method) were recorded. Also, Gillette Functional Walking Scale (GFWS) was completed by parents for practical assessment of walking.

*Results.* FOF results were 16.75 ± 8.12 over a total of 64. No statistically significant differences were found between FOF and step length, stride length, and step width ($p > 0.05$). Positive, strong, statistically significant correlation was determined between FOF and stance width ($p = 0.012$, $r = 0.610$) while negative, strong correlations were found between FOF and walking speed ($p = 0.011$, $r = -0.633$), and GFWS ($p < 0.01$, $r = -0.673$).

*Conclusions.* It was determined that stance width, walking speed, and functional walking ability were the main factors that affect fear of falling of children with DMD.

## Investigation of history of falls and fear of falling in children with Duchenne muscular dystrophy: a pilot study

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*Objective.* This study was planned to investigate history of falls and its effects on fear of falling (FOF) in children with Duchenne muscular dystrophy (DMD).

*Method.* Sixteen ambulatory children with DMD between 6-15 years of age were included in the study. FOF was assessed by using "ICF Based Fear of Falling Assessment in Pediatric neuromuscular diseases" (IBFOF) which was developed by the researchers of current study considering the ICF domains and fear of falling assessments in the literature. The total score ranged between 0-68 which higher scores indicate higher degrees of fear of falling. History of Falls Questionnaire (HFQ) was used to assess falling history of children over the past year. Falling frequencies over the last week were also recorded.

*Results.* The mean scores of FOF was found 16.75 ± 8.12. Activities at which most serious falls occur were found as running (25%), doing sports (12.5%), climbing stairs (6.3%), walking (43.8%), getting on/off toilet (6.3%), and standing (6.3%). The location of most serious falling experienced were determined outdoor with 68.8 ratio. 62.5% of all subjects reported an injury caused by falls and falling frequencies of children were found as 3 per week. The factors related to falling history such as activity, locations, falling frequency, and injury caused by falling were not correlated with FOF in children with DMD ($p > 0.05$).

*Conclusions.* It was determined that the children in our study did not experience higher degrees of falling fear with lower falling frequency in our study. Falling history was not determined to have an effect on fear of falling of ambulatory patients with DMD. The results may change when the patients with higher falling frequencies are included to our ongoing study. Nevertheless, other factors related to fear of falling rather than falling history should also be investigated more comprehensively in further studies.

## Investigation of the relationship between activity limitation and upper extremity performance in non-ambulatory patients with Duchenne muscular dystrophy

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*Objective*. It is known that activities of children with Duchenne muscular dystrophy (DMD) using wheelchairs are limited. Thus, the functional use of their upper extremity is important to be able to sustain the activities of daily living. However, it is not known how much relation between activity limitations of children and their upper extremity performances. The aim of our study was to investigate the relationship between activity limitation and upper extremity performance in non-ambulatory children with DMD.

*Method.* Twenty-three non-ambulatory patients with DMD from level 1-5 according to Brooke Upper Extremity Functional Classification (BUEFC) were included in our study. Their activity limitations were assessed by ACTIVLIM (0-36), hand functions by ABILHAND-Kids (0-36), upper extremity performances by Performance of the Upper Limb (PUL) (0-74) which evaluate upper extremity performances at 3 levels, including shoulder, elbow, hand-wrist.

*Results.* The mean age of the children included in the study was 13.04 ± 1.39 years and the mean duration of wheelchair usage was 28.43 ± 15.58 months. Children's ACTIVLIM scores were moderate correlated with BUEFC scores negatively ($-0.656$, $p = 0.001$), and with PUL (shoulder) score positively ($r = 0.623$, $p = 0.002$), and strongly correlated with PUL (elbow) ( $= 0.802$, $p < 0.001$), PUL (total) ($r = 0.749$, $p < 0.001$) and ABILHAND-Kids ($r = 0.888$, $p < 0.001$) scores positively.

*Conclusions.* In our study, it was determined that general upper extremity and hand functions strongly affected the activity limitations in non-ambulatory children with DMD and it emphasized the necessity of intensely practice of therapy approaches that increase the function of upper extremity in non-ambulatory period.

## Which one has the most effect on performance in children with Duchenne muscular dystrophy?: shortness, flexibility and/or muscle strength of hamstrings

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*Purpose.* The aim of this study was to determine which physical characteristic of hamstrings such as shortness, flexibility and/or muscle strength has the most effect on performance in children with Duchenne muscular dystrophy (DMD).

*Methods.* Thirty children with DMD were included in the study. Children's functional level was determined by the Brooke Lower Extremity Functional Classification (BLEFC). Hamstrings shortness was evaulated by Straight Leg Raise Test, flexibility by Popliteal Angle Test, and muscle strength by myometer. Children's performance was determined by calculating the distance in 6 Minute Walk Test (6MWT). The correlations between these characteristics of hamstring muscles and performance were analyzed with Spearmans's and Pearsons Correlation Coefficient.

*Results.* The mean age of children was 7.77 ± 2.03 years. Nineteen children were in level 1 and 11 children in level 2 ac-

cording to BLEFC. The mean shortness score of hamstrings was 69.2 ± 11.59°, flexibility score was 60 ± 30°, and muscle strength score was 9.12 ± 2.5N, and the mean distance in 6MWT was 394.55 ± 63.77 m. There was a negative excellent, statistically significant correlation between Popliteal Angle Test (flexibility of hamstings) and 6 MWT ($r = -0.825$, $p < 0.001$). There was not any correlation between other characteristics of hamstrings and performance.

*Discussion.* In this study, it was determined that the main factor affecting performance in DMD is the hamstrings flexibility rather than shortness and strength. This result indicates that hamstrings' flexibility should be evaulated and the exercises to maintain/increase the flexibility of hamstrings should be considered in physiotherapy programs in each period of the disease in DMD.

## Profile of patients with spinal muscular atrophy in turkey: an analyze from KUKAS Registry System

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*Objective.* The aim of this study was to determine the profile of patients with spinal muscular atrophy (SMA) who registered to Registry System of Patients with neuromuscular diseases in Turkey (KUKAS).

*Method.* Web page and software for the KUKAS registry system were developed in January 2011. Since this date, the demographic and assessment data of the patients with Duchenne muscular dystrophy (DMD) and SMA were recorded in this system. The total number of SMA patients and the ratios according to the type of SMA, genetic test confirmations, and distribution according to gender and geographical regions of the SMA patients as well as the consanguinity between parents were investigated from the registry system.

*Results.* Over a total of 439 patients (55% male, 45% female) with SMA who registered to the KUKAS, 193 patients were determined as Type 1, 164 Type 2, 78 Type 3, and 4 patients as Type 4. Genetic tests of 229 patients were found to be recorded to the system. According to geographical regions of Turkey the distribution of registered patients were listed as follows; 9.38% Mediterranean Region, 6.17% Aegean Region, 20.49% Marmara Region, 11.11% Black Sea Region, 40.24% Central Anatolia Region, 7.16% Eastern Anatolia Region, and 5.18% Southeastern Anatolia Region. Fourteen percent of the parents were relative.

*Conclusions.* According to official records, it is estimated that there are approximately 2500 SMA patients in Turkey. The number of patients registered to our system may be considered as good rate for a single center. SMA patients have been more tend to register to KUKAS in recent years by the advances in drug treatments for SMA.

## Comparison of the effect of aquatherapy and cycle ergometer training in a child with spinal muscular atrophy type II: a case report

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*Objective.* Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by degeneration of alpha motor neurons in the spinal cord. Until recently, no clear treatment of the disease, while nusinersen, an antisense oligonucleotide, was approved for all types of SMA in the last year. Currently it is only given for SMA type 1 in Turkey. This study was aimed to examine the effect of aquatherapy and cycle ergometer training in a boy with SMA type 2 whose age was five.

*Method.* Motor Functions were measured with Hammersmith Functional Motor Scale (HFMS) and Gross Motor Function Measure (GMFM-88). Pulmonary function was assessed by spirometry and treatment satisfaction of the child and parent was questioned with numerical rating scale (from 0 to 10 points). Firstly, cycle ergometer training was applied three times per week for 12 weeks. Aquatherapy (Halliwick Concept) then started for twice a week for 12 weeks following 6 weeks washout period. He was followed for one year after both exercises.

*Results.* After ergometer training, the HFMS score improved by 21.7%, the GMFM total score by 63.4% and also pulmonary function was preserved. The HFMS score improved by 11.5% and the GMFM total score by 37,5% following aquatherapy. Similar to results of ergometer training, pulmonary function was maintained. These improvements was largely preserved during one year. Cycle ergometer training satisfaction of the child and parent was 6 and 5 points while aquatherapy satisfaction was 7 and 8 points, consecutively.

*Conclusions.* It has been emphasized that these protective and improving effect of alternative methods such as aerobic exercise are important in terms of increasing the possibility of involving SMA patients in future clinical trials and the effectiveness of these trials. It will be a guide for researchers working with children with neuromuscular disorders.

## Nusinersen and early physiotherapy in patients with spinal muscular atrophy type 1: case series

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*Objectives.* To evaluate effects of combined of nusinersen and early physiotherapy on functional performance, respiratory and nutritional status in four cases with SMA type 1.

*Method.* The children was three females and one male, aged from 10 month to 5 years 9 month. One patient used nasal CPAP, 3 patients benefited from mechanical ventilation with tracheotomy and one patient had gastrostomy at baseline. All patients underwent a physiotherapeutic evaluation at the time of the first consultation (pre-treatment) as well as on the follow up-visit (8 week intervals for 24 weeks). CHOP INTEND is used to evaluate functional performance. The primary endpoint of cases was change in CHOP INTEND score from baseline. As secondary endpoint, we evaluated changes in respiratory and nutritional status as well as parents' impression regarding improvements or worsening in motor and respiratory function. To evaluate parents' impression, we used a Likert scale with five categories. Intrathecal Nusinersen was applied 4 doses. Physiotherapy program were done 2 days in a week for 24 week supervised by physiotherapist and home exercises were given on other days.

*Results.* After 4 doses nusinersen and early physiotherapy, mean improvement of CHOP INTEND score was 10.7 ± 2.21 points, MV pressure was reduced three patient, a patient was

observed to need nasal CPAP during sleep only. Nutritional status and parents' impression were improved. Parents of 3 children reported a marked improvement and parents of 1 children a slight improvement in motor function, regarding respiratory function an improvement, parents of 3 children a marked improvement and parent of 1 children did not observe a change. *Conclusions.* Depending the improvements after nusinersen and early physiotherapy, we believe that the prospective follow up of this data will bring information about benefit ratio of nusinersen and early physiotherapy in this population.

## Correlation between fonctional ambulation classification (FAC) levels and serum vitamin B12 levels in myotonic patients

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*Aim.* The aim of this study was to evaluate correlation between functional ambulation classification (FAC) levels and serum vitamin B12 levels in myotonic patients.

*Material and methods.* A retrospective cross sectional study was conducted in neuromuscular diseases Unit of Izmir Tepecik Training and Research Hospital. The clinical data containing demographic variables, FAC levels and serum vitamin B12 were recorded from the files of patients. Fatigue symptoms which were questionned before were evaluated. It was recorded whether there has been a fall in the last 6 months.

*Results.* A total of 53 patients (26 female, 27 male) were included in this study. The mean age was 31,13 ± 15,32. There were 34 patients diagnosed with myotonic dystrophy, 13 patients diagnosed with myotonia congenita and 6 patients diagnosed with myotonia. There were 34 patients with fatigue symptoms. 75,5% of patients was FAC level 4 and above The median serum vitamin B12 levels was 235,5 (94-2000). There were 18 patients who had fallen in the last 6 months. There was no correlation between FAC levels and serum vitamin B12 levels in myotonic patients ($r = 0.069$, $P > 0.05$)

*Conclusions.* The results of our study suggest that there is no correlation between FAC levels and serum vitamin B12 levels in myotonic patients.

## Complementary and alternative therapies in neuromuscular diseases

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Complementary and alternative medicine (CAM) is the term for medical products and practices that are not part of standard medical care neuromuscular diseases are neurons, neuromuscular junctions and muscular diseases that move our bodies. The most important findings are numbness, burning, tingling, weakness and muscle cramps. They are clinically progressive and medical treatment is limited. For this reason, medical treatment and rehabilitation can be applied to complementary alternative therapies.

*Aim.* To evaluate the use of Complementary and Alternative Therapy methods (CATM) in neuromuscular disease (NMD), which are used frequently.

*Material and methods.* Patients and their caregivers who were followed up at the neuromusculer diseases unit and department of physical medicine and rehabilitation were included in the study. Demographic data of the patients (age, gender, education, economic status), functional activity scores, wheelchair usage were questioned. Participants (adult and their caregivers) were completed a questionnaire assessing their attitude and use of complementary and alternative treatments.

*Results.* A total of 246 patients, 96 (39%) women, 150 (61%) men were included in this study. 108 patients used complementary and alternative therapy methods. Patient-specific diet, nutritional support, mental body treatments, manupulative techniques and energy techniques were questioned. The most commonly used theraphy method was dietary supplements (74,1%). CATM use was statistically significantly higher in patients with high socioeconomic status and low education status. ($p = 0,044$). There was a statistically significant relationship between wheelchair use and CATM usage. The percentage of patients who benefit CATM was 48,6%.

*Conclusions.* Complementary and alternative therapy methods use was common in our patients diagnosed with neuromuscular disease. The most commonly used theraphy method was dietary supplements.

## Wheelchair evaluation of neuromuscular diseases

Turanoglu M.[1], Sertpoyraz F.M.[1], Dikici A.[2], Ozer S.[3]
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*Aim.* to evaluate the wheelchairs suitability to the patient-*Materials and methods*. Cross-sectional study patients were included in the study, who applied to the Department of Health Sciences, Izmir Tepecik Education and Research Hospital, Norumuskuler Diseases Unit,in 2017-2018 Demographic data, clinical findings of patients, and wheelchair usage were questioned. There were 5 female and 21 male patients in study. Diagnostic groups were identified. There were 22 patients with muscular disease, and 4 patients with nervous disease.Diagnoses included 14 Duchenne muscular dystrophy, 1 limb-girdl muscular dystrophy, 2 spinal muscular atrophy, 2 PNP, 1 myopathy, 5 others. The wheelchair is only suitable for one patient, not 25 patients.

# AUTHOR INDEX

# NEWS FROM AROUND THE WORLD

## AIM

The XVIII Congress of the Italian Association of Myology was held in Genoa last 6-9 June. It was organized by Prof. Carlo Minetti and coworkers in the three-days traditional format.

This year a special event was celebrated, the 18-year anniversary of the Association. The attendance of the participants over the years has been steadily increasing, with the single sessions in the hall and the posters sessions always overcrowded.

Particularly appreciated was the joint session with the Société Française de Myologie, which dealt with the same topics with different viewpoints and experiences. During the congress, there was the election of the new board of the Association and of the new President.

In the next issues of Acta Myologica we will give you more details.

## MSM

The 13th Congress of the Mediterranean Society of Myology will be held in Turkey on 27-29 June 2018, organised by Prof. Haluk Topaloglu. The symposium was in the traditional two-days MSM format with selected topics (see brochure). During the Gala dinner of the 13th Congress of the Mediterranean Society of Myology the 2018 Gaetano Conte Prizes will be assigned for basic and clinical research.

## WMS

The 23rd International WMS Congress will be held in Mendoza, Argentina from 2 to 6 October 2018. The symposium will follow the traditional format with 3 selected topics:

new developments in genetic and acquired disorders of the neuromuscular junction;

mitochondrial function and dysfunction in neuromuscular disorders: pathogenesis and therapies;

advances in the treatment of neuromuscular disorders.

One day of the symposium will be dedicated to each of the selected topics. Invited keynote speakers will summarize the state of the art on the selected topics, covering clinical, molecular and other aspects. The sessions will comprise selected oral papers and poster presentations with guided discussions. Contributions will also be welcome on new advances across the neuromuscular field. The 16th WMS Pre-Congress Teaching Course will be held on 1-2 October 2018. Please note only 45 places are available. Early booking is advised

# FORTHCOMING MEETINGS

## 2018

**June 06-09**

18th National Congress of Italian Association of Myology. Genua, Italy. Information: website: *www.miologia.org*

**June 16-19**

European Human Genetics Conference 2018. Milan, Italy. Information: website: *conference@eshg.org*

**June 16-19**

4th Congress of the European Academy of Neurology. Lisboa, Portugal. Information: *website: www.ean.org*

**June 27-29**

XIII Congress of Mediterranean Society of Myology. Avanos, Cappadocia, Turkey. Information: *msm2018@flaptour.com.tr; htopalog@hacettepe.edu.tr*

**July 6-10**

15th International Congress on Neuromuscular Diseases (ICNMD2018), Wien, Austria. Information: *www.icnmd2018.org*

**August 25-29**

European Society of Cardiology (ESC). Munich, Germany. Information: website: *https://www.escardio.org*

**October 2-6**

23rd Congress of World Muscle Society. Mendoza, Argentina. Information: website: *www.worldmusclesociety.org*

**October 16-20**

ASHG Annual Meeting. San Diego, CA,USA Information: website: *www.ashg.org*

**October 17-21**

Asia Pacific Heart Rhythm Society (APHRS). Taipei, Taiwan. Information: website: *http://www.aphrs.org*

**October 24-25**

9th World Congress on Targeting Mitochondria,Berlin, Germany. Information: website: *https://targeting-mitochondria.com*

**October 31 - November 02**

World Congress on Human Genetics. Valencia, Spain. Information: website: *http://humangenetics.conferenceseries.com*

**November 9-10**

9th International Conference & Exhibition on Tissue Preservation and Biobanking. Atlanta, USA, during 2018. Information: website: *http://biobanking.conferenceseries.com*

## 2019

**May 2019**

Heart Rhythm 40th Annual Scientific Sessions (HRS). Chicago, IL. Information: website: *http://www.hrssessions.org/*

**June 15-18**

The European Human Genetics Conference 2019. Gothenburg, Sweden. Information: *conference@eshg.org*

**September 24-28**

24th Congress of World Muscle Society. Copenhagen, Denmark. Information: website: *www.worldmusclesociety.org*

**October 22-26**

ASHG Annual Meeting. Toronto, Canada. Information: website: *www.ashg.org*

**To be announced**

Asia Pacific Heart Rhythm Society (APHRS). Bangkok, Thailand. Information: website: *http://www.aphrs.org*

## 2020

**June 6-9**

The European Human Genetics Conference 2020, Berlin, Germany. Information: *conference@eshg.org*

**October 27-31**

ASHG Annual Meeting. San Diego, CA,USA .Information: website: *www.ashg.org*

**To be announced**

25th Congress of World Muscle Society. Toronto, Canada. Information: website: *www.worldmusclesociety.org*

## For application or renewal to MSM

**MEDITERRANEAN SOCIETY OF MYOLOGY* (MSM)**

H. Topaloglu, *President*
L.T. Middleton, G. Siciliano, *Vice-Presidents*
K. Christodoulou, *Secretary*
L. Politano, *Treasurer*

APPLICATION/RENEWAL FORM

**Application/Renewal for** **1yr** ☐ **2 yrs** ☐

Prof. Luisa Politano, Cardiomiologia e Genetica Medica, Primo Policlinico, piazza Miraglia, 80138 Napoli, Italy
Fax: 39 081 5665101 E-mail: actamyologica@gmail.com • luisa.politano@unicampania.it
Fax or Mail to the above address. Type or print.

Name _____ Degree(s) _____
Last First

Department _____ _____

Institution _____

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City, State, zip, country _____

Tel (_____) _____ Fax (_____) _____
Area code Area code

* Amount payable: 1 year Euro 100
2 years Euro 150

❑ I enclose copy of the bank transfer to:

Bank name: Banco di Napoli – Filiale 00660
Bank address: Via Riviera di Chiaia, 131 – 80122 Napoli, Italy
Account holder: MSM – Mediterranean Society of Myology
IBAN code: IT48T0101003488100000100680
BIC code (for foreign countries): IBSPITNA

# INSTRUCTIONS FOR AUTHORS

***Acta Myologica*** publishes articles related to research in and the practice of primary myopathies, cardiomyopathies and neuromyopathies, including observational studies, clinical trials, epidemiology, health services and outcomes studies, and advances in applied (translational) and basic research.
Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within eight weeks. All rebuttals must be submitted in writing to the editorial office.

**On-line submission**
Manuscript submission must be effected on line: **www.actamyologica.it** according to the following categories:
*Original articles* (maximum 5000 words, 8 figures or tables). A structured abstract of no more than 250 words should be included.
*Reviews, Editorials* (maximum 4000 words for Reviews and 1600 words for Editorials). These are usually commissioned by the Editors. Before spontaneously writing an Editorial or Review, it is advisable to contact the Editor to make sure that an article on the same or similar topic is not already in preparation.
*Case Reports, Scientific Letters* (maximum 1500 words, 10 references, 3 figures or tables, maximum 4 authors). A summary of 150 words may be included.
*Letters to the Editor* (maximum 600 words, 5 references). Letters commenting upon papers published in the journal during the previous year or concerning news in the myologic, cardio-myologic or neuro-myologic field, will be welcome. All Authors must sign the letter.
*Rapid Reports* (maximum 400 words, 5 references, 2 figures or tables). A letter should be included explaining why the author considers the paper justifies rapid processing.
*Lectura*. Invited formal discourse as a method of instruction. The structure will be suggested by the Editor.
*Congress Proceedings* either in the form of Selected Abstracts or Proceedings will be taken into consideration.
Information concerning new books, congresses and symposia, will be published if conforming to the policy of the Journal.
The manuscripts should be arranged as follows: 1) Title, authors, address institution, address for correspondence; 2) Repeat title, abstract, key words; 3) Text; 4) References; 5) Legends; 6) Figures or tables. Pages should be numbered (title page as page 1).
*Title page.* Check that it represents the content of the paper and is not misleading. Also suggest a short running title.
*Key words*. Supply up to three key words. Wherever possible, use terms from Index Medicus – Medical Subject Headings.
*Text.* Only international SI units and symbols must be used in the text. Tables and figures should be cited in numerical order as first mentioned in the text. Patients must be identified by numbers not initials.
*Illustrations.* Figures should be sent in .jpeg or .tiff format. Legends should be typed double-spaced and numbered with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each should be explained clearly in the legend. For photomicrographs, the internal scale markers should be defined and the methods of staining should be given.
If the figure has been previously published a credit line should be included and permission in writing to reproduce should be supplied. Colour photographs can be accepted for publication, the cost to be covered by the authors.
PATIENTS IN PHOTOGRAPHS ARE NOT TO BE RECOGNISABLE
*Tables*. Tables should be self-explanatory, double spaced on separate sheets with the table number and title above the table and explanatory notes below. Arabic numbers should be used for tables and correspond with the order in which the table is first mentioned in the text.
*References.* Reference numbers in the text must be in brackets. References in the list must be numbered as they appear in the text.
Standard journal article: Figarella-Branger D, Bartoli C, Civatte M, et al. Cytokines, chemokines and cell adhesion molecules in idiopathic inflammatory myopathies. Acta Myol 2000;19:207-8.
Books and other monographs: Dubowitz V. Muscle disorders in childhood. London: WB Saunders Company Ltd; 1978.
Please check each item of the following checklist before mailing:

- Three index terms, short title for running head (no more than 40 letter spaces) on the title page.
  Name(s) of the author(s) in full, name(s) of institution(s) in the original language, address for correspondence with telephone and fax numbers and email address on the second page.
- Summary (maximum 250 words).
- References, tables and figures cited consecutively as they appear in the text.
- Figures submitted actual size for publication (i.e., 1 column wide or 2 columns wide).
- Copyright assignment and authorship responsibility signed (with date) by all Authors.
- References prepared according to instructions.
- English style.
- Patients in photographs not recognisable.