CONGENITAL MYASTHENIC SYNDROMES: EXPERIENCE ON A LARGE COHORT FROM A SINGLE QUATERNARY CENTRE FOR NEUROLOGICAL DISORDERS IN INDIA

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Background: Congenital myasthenic syndromes (CMS) are heterogeneous, treatable inherited neuromuscular junction (NMJ) disorders which are frequently un/misdiagnosed.

Methods: We describe 59 cases based on clinical, electrophysiological findings and pharmacological response, and 20 genetically confirmed patients (2010-2017).

Results: All had fatigable muscle weakness, almost all having preserved/exaggerated tendon reflexes. Several had persistent muscle weakness suggesting myopathy but with diurnal/seasonal/prolonged fluctuations. All demonstrated significant decremental response and responded well to either pyridostigmine/salbutamol/fluoxetine or combinations.

Mutation positive group: M:F=1.1:1. Consanguinity=11/20, affected siblings=7 families. Onset: birth/infancy/early childhood=16 (5/20 had feeble cry), second decade=3, third decade=1. Mean age at onset=4.7±7.5 years (range, birth-28); age at presentation=19.9±14.4(1-48); illness duration=15.4±11.9(0-46). Initial symptom: ocular=12; bulbar=2; upper/lower limb weakness=7. Phenotypes: generalised=8; ocular(ptosis+ophthalmoparesis)=4; oculobulbar=1; limb girdle+ptosis without ophthalmoparesis=5; limb girdle=2. Homozygous mutations in AChR epsilon subunit (CHRN ε) defect=12, kinetics of CHRN ε (fast channel)=1, DOK7=5, RAPSYN=1, MuSK=1. Homozygous c.1327delG mutation in CHRN ε (5/12, novel=7. Most common DOK7 mutation=c.1124_1127dup TGCC in 4/5; one novel. MuSK gene mutation was novel. DOK7/MuSK cases responded well to salbutamol/Fluoxetine, remaining to pyridostigmine and salbutamol.

Genetically unconfirmed: M:F=1.2:1. Consanguinity=27/59, affected siblings=20 families. Onset: infancy/early childhood=47 (13/59 had feeble cry); second decade=9, third decade=3. Mean age at onset=4.4±6.5 years (birth-29); age at presentation=17.3±11.1(1-51); illness duration=12.6±10.7(0-49). Phenotypes at presentation: only ptosis=5; ocular(ptosis+ophthalmoparesis)=9; oculobulbar=1; generalised=26; limb girdle+ptosis without ophthalmoparesis=3; limb girdle=15. Seizures in 4; MR=6; Possible diagnosis of SNAP25=2; DPAGT1=3; other glycosylation defects=11. Mean CK level=363.8±1109.7U/L (27-7247).

Conclusion: CHRN ε defect was the commonest form followed by DOK7. Meticulous history/examination are crucial in diagnosing CMS as many have associated myopathic features and infrequently elevated CK.
Background: Dystrophinopathies constitute Duchenne (DMD) and Becker (BMD) muscular dystrophies resulting from mutations in DMD gene (Xp21). MLPA (Multiplex Ligation-dependent Probe Amplification) detects CNVs (deletions and duplications) comprising 75% of mutations. Remaining 25% mostly include SNVs (point mutations) and INDELs which require direct sequencing.

Objective: To identify CNVs and point mutations in DMD/BMD patients using Targeted Next Generation Sequencing (NGS).

Methodology: Diagnosis was confirmed by either MLPA or muscle immunohistochemistry (IHC). After obtaining informed consent/assent, DNA was extracted from blood samples of ten patients for sequencing. Two custom panel designs were tested for target capture of DMD gene using SureselectXT (Agilent) method and sequencing with 150x2 chemistry on NextSeq 500 (Illumina). First design constituted high density probes covering entire DMD gene with total capture size: 2.077M bp. Second design comprised of high density probe set covering exonic and promoter regions of DMD and other muscular dystrophy genes. A low-resolution backbone probe set covering intronic region was included to create a much-reduced total capture size of 408.133Kbp.

Results: MLPA confirmed cases with deletions: 5 (50%); Biopsy confirmed cases: 5 (50%). Both NGS panels showed good efficacy in detection of deletions and SNVs. NGS identified mutations in 9/10 DMD cases (90%). Concordance rate of NGS results was 100% in MLPA positive cases, with accurate intronic breakpoint information. In one case where MLPA showed ambiguous result, NGS clearly detected deletions which was further confirmed by PCR. Pathogenic non-sense mutations were identified in three cases and one of them is a novel variant.

Conclusion: Targeted NGS offers a sensitive and cost effective single platform diagnostic method for diagnosis of Dystrophinopathies.
tapping test = 88%; Stroop test = 56.3%; Colour Trail 1 (CT1) = 47%; CT2 = 40%; Digit vigilance = 40%; Complex figure test = 37%.
Significant correlation between motor speed and Mayo SQ; mental speed, CT2 and HAM-D. Cerebral atrophy in 13, ventricular enlargement = 10, white matter hyperintensities = 8. VBM showed significant grey matter (GM) atrophy compared to controls [right prefrontal gyrus, left thalamus, left rectal gyrus]. Negative correlation between GM and duration of illness (left median frontal gyrus), CT2 (left frontotemporal lobe, caudate). FSL–Reduced fractional anisotrophy in corpus callosum, bilateral corona radiate, internal capsule, cingulum and cerebellar peduncles.

Conclusion: Neuropsychology revealed impaired motor speed, attention, executive function and visuo-constructive deficits. MRI demonstrated significant white and grey matter abnormalities and definite correlation with cognitive performance.

MUSK ANTIBODY ASSOCIATED REVERSIBLE FORM OF MOTOR NEURON DISEASE MIMIC: PRESENCE OF PROMINENT FACIAL AND JAW MUSCLE INVOLVEMENT

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Background: MuSK-MG can present as chronic progressive bulbar palsy (PBP) and/or dropped head syndrome, limb weakness and wasting which could easily be mis-diagnosed as motor neuron disease (MND).

Materials and Methods: We describe 7 interesting anti-MuSK antibody positive patients (January 2016 to April 2017) with symptoms and signs typical of MND but with certain characteristic markers. MuSK antibody testing was performed by ELISA method according to commercial MuSK, IBL International guidelines. Antibodies were identified by HRP conjugated mouse anti-human IgG4 and chromogenic substrate and measured at 492 nm as OD.

Results: M:F = 2.5:1. Mean age of onset = 59.0 ± 7.9 years (range, 48-71); age at presentation = 72.0 ± 7.8 years (49-72), duration of illness = 15.2 ± 15.3 months (3-48); dysarthria (7/7) = 14.1 ± 16.3; anarthria (3/7) = 4.8 ± 8.7; dysphagia (6/7) = 8.7 ± 12.6; nasal twang (6/7) = 4.6 ± 5.3; profuse sialorrhoea (5/7) = 2.7 ± 3.8 months. Severe weight loss = 3/7. Mean duration of tongue wasting with reduced movements (5/7) = 7 ± 7.4 months. Jaw jerk brisk = (6/7); facial fasciculations (5/7) and limb fasciculations (3/7). All had prominent chin fasciculations with a corrugated/puckered appearance of mentalis muscle and severe lower facial weakness. Wasting with weakness of temporalis, masseters and facial muscles = 6 cases. Emotional lability = 6/7 cases. Five had wasting and weakness of upper limbs (distal-5 with minipolymyoclonus; proximal-2). Hyperactive tendon reflexes present in all. Tongue MRI in two cases showed fatty infiltration. 6/7 showed satisfactory response to either pyridostigmine/oral steroids/ plasmapheresis/cyclophosphamide.

Conclusion: We report 7 unusual anti-MuSK antibody positive MND mimics. Typically all had presence of severe lower > upper facial wasting and weakness along with trigeminal motor involvement and intense sialorrhoea. Chin showed puckered appearance with fasciculations. Important to identify these MND mimic as it is potentially reversible.

HANSEN’S DISEASE: EVIDENCE OF BRAIN AND SPINAL CORD LESIONS AND INVOLVEMENT OF RADICULO-PLEXII ON MR IMAGING

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**Objectives/Background:**
Hansen’s disease has a predilection to involve skin and distal peripheral nerves. Lesions in proximal nerves or plexus are very rarely described, but lesions in central nervous system (CNS) and spinal cord is never reported. Here we document exceptional imaging findings on MRI in pathologically confirmed cases of Hansen’s disease.

**Materials and Methods:** MR neurography (MRN) of brachial (BP) and lumbosacral plexii (LSP), spine and brain MRI with contrast sequences were performed in 9 patients confirmed to have Hansens disease.

**Results:** Nine patients, age range = 17–47 years, mean illness duration = 24.11 months were classified as tuberculoid (2), borderline tuberculoid (5) and borderline lepromatous (2) based on nerve biopsy. All had sensory-motor deficits. Hypopigmented and hypoesthetic skin lesions = 6 cases. MRN showed thickening of BP in 8 cases and of LSP in 4. Contrast enhancement in 4 with one having right L3 root abscess and another having swelling of right cervical radicles. Spine MRI showed T2 hyperintense lesions in cervical cord (3), cervico-dorsal region (1) and conus (1). Contrast enhancement with cord swelling occurred in 3 patients. Symmetry and location of cord and plexii lesions corresponded with clinical deficits. Brain MRI was done in 7 cases. One patient with 10 years illness had severe bifacial weakness and demonstrated enhancing lesions in facial nerve nuclei, his radial nerve showed Lepra DNA by PCR and Rifampicin resistance by Gene Sequencing.

**Conclusion:** While mono-neuritis multiplex is the commonest presentation in Hansen’s neuritis, we describe extraordinary involvement of radicles and plexii along with hitherto unreported Brain and spinal cord lesions on MR imaging. All patients manifested with only distal peripheral nerve disease.

**TARGETED NEXT GENERATION SEQUENCING IN UNDIAGNOSED EARLY-ONSET NEUROMUSCULAR DISORDERS**

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**Objectives/Background:** Neuromuscular disorders are clinically, pathologically, and genetically heterogeneous groups of disorders. Particularly during infancy and childhood, the clinical presentation shares similar features such as hypotonia, weakness, and motor developmental delay, which make it difficult to reach a specific diagnosis even for the experienced clinicians. An accurate genetic diagnosis has often been challenging due to the heterogeneity and complexity of these groups of disorders. The advent of next generation sequencing (NGS) technologies have started a new era of molecular genetic diagnosis in neuromuscular disorders. It is an effective diagnostic tool for the parallel investigation of a large number of genes and has been increasingly used in the recent clinical and research fields.

**Materials and Methods:** We applied an NGS-based platform to the diagnostic workflow in the genetic characterization of patients with early onset neuromuscular disorders. We have set up the targeted sequencing panels cover 434 causative genes known for hereditary neuromuscular disorders.

**Results:** Total 196 cases with undiagnosed early-onset neuromuscular disorders were analysed and one third of them (n = 65) were genetically confirmed up to date. A further 74 cases had unproven candidate variants as yet. Pathogenic variants were found in 43 of 434 genes.

**Conclusion:** Our study illustrates the clinical utility of targeted NGS as a powerful diagnostic tool in early-onset hereditary neuromuscular disorders. It can be advantageous as a first-tier test in view of less-invasive clinical approach, diagnosis speed, and cost-effectiveness.

**MYOSITIS ANTIBODY PROFILE IN A TERTIARY NEUROMUSCULAR LABORATORY**

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**Objectives/Background:** To study the relative frequencies of myositis-specific and myositis-associated autoantibody in a tertiary neuromuscular laboratory in Singapore.
Materials and Methods: We retrospectively analysed the results of requests for myositis auto-antibody tests from January 2015 to December 2016 at our laboratory, a tertiary neuromuscular service centre serving various hospitals in Singapore. The myositis panel consists of 16 auto-antibodies against Mi-2, TIF1g, MDA5, NXP2, SAE1, Ku, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52 and proteins of the nucleolar PM-Scl macromolecular complex (PM-Scl100 and PM-Scl75).

Results: We received blood samples of 206 patients during this period. 44.7% of tests were positive for at least one autoantibody, 15.5% for two, 2.4% for three and 1% for four. The most common autoantibody was anti-Ro-52 (24.3%), followed by anti-TIF1g (7.8%), anti-PM/ScI75 (6.8%), anti-SRP (5.8%), anti-MDA5 (5.8%), anti-Ku (4.4%), anti-Jo-1 (3.4%), anti-Mi-2 (3.4%), anti-PL-7, anti-NXP2 (1.9%), anti-PM/ScI100, PL-12 (1.5%), anti-EJ (1%) and anti-SAE1 (0.5%). Anti-OJ antibody was not found in any. Among the 50 anti-Ro-52 positive patients, about two-thirds (33) had 1 to 3 other myositis-specific or myositis-associated antibodies. The most common were TIF1g (6), PM-ScI75 (6), MDA5 (5), SRP (4) and Jo-1 (4).

Conclusion: Just under half the tests for the abovementioned 16 myositis-specific or myositis-related antibodies were positive. The commonest autoantibody detected is anti-Ro-52, often associated with TIF1g, PM-ScI75, MDA5, SRP and Jo-1 antibodies. In the next phase of the study we shall correlate the clinical features, pathological findings and treatment response of the antibody positive patients with their specific serological profile.

MYOTUBULAR/CENTRONUCLEAR MYOPATHY PATIENT REGISTRY: ACCELERATING THE PACE OF RESEARCH AND TREATMENT

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Objectives/Background: The Myotubular/Centronuclear Myopathy (MTM/CNM) Patient Registry is an international, patient-reported, disease-specific registry, established in March 2013.

Materials and Methods: Registrations are accepted from patients, parents-guardians of patients, female carriers of X-linked myotubular myopathy (XLMTM), and from family members who wish to register deceased patients. After initial registration, online consents must be completed before access is given to the rest of the questionnaires including clinical information. Patients' genetic and/or muscle biopsy reports can be uploaded if available.

Results: As of February 2017, 188 participants had registered from 27 countries, and 145 had consented (122 patients and 23 XLMTM female carriers). Out of 122 patients, 98 patients reported to be diagnosed as MTM (64 males, 2 females) or CNM (19 males, 11 females) both pathologically and genetically. Genetic mutations were identified in myotubularin (MTM1) (n=62), dynamin-2 (n=15), ryanodine receptor-1 (n=3), bridging integrator-1/amphiphysin-2 (n=2), or titin (n=1). The median deceased age among 18 patients with MTM1 was 2.5 years old. The clinical features were varied among female carriers as well as among patients with mutations in the same gene.

Conclusion: The registry contains a significant amount of data from diverse and growing cohorts of MTM/CNM patients, and provides means of accessing and analysing a cross-sectional snapshot of the international patient population. It can help to identify and recruit patients into all aspects of clinical research, and aims to assist and support a collaborative effort between clinicians, researchers and patient groups to increase our understanding of these conditions and enhance trial readiness in the patient population.

RD-CONNECT: DATA SHARING AND ANALYSIS FOR RARE DISEASE RESEARCH

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Objectives/Background: Research into rare diseases is typically fragmented by data type and disease. Individual efforts often have poor interoperability and do not systematically connect data across clinical phenotype, genomic data, biomaterial availability, and research/trial data sets. Such data must be linked at both an individual-patient and whole-cohort level to enable researchers to gain a complete view of their disease and patient population of interest.

Materials and Methods: RD-Connect is a global infrastructure resource initiated in 2012 and funded by the European Union. It is a platform for rare disease research and gene discovery bringing together multiple omics data types (genomics, proteomics, transcriptomics) with biosample and clinical information at individual-patient, family or whole-cohort level. It provides both a centralized data repository and a user-friendly online analysis system. Whole-genome, exome or gene panel data are deposited at the European genome-phenome Archive for long-term storage, then processed by RD-Connect’s standardized analysis and annotation pipeline to make data from different sequencing providers comparable. Researchers from any RD research project or clinical center worldwide can submit data, analyze their own patients and compare with data submitted by other centers. Clinical information is recorded in PhenoTips, simplifying data entry using the Human Phenotype Ontology.

Results and Conclusion: The online platform contains data from almost 3000 individuals, including a large number of neuromuscular and neurodegenerative phenotypes (LGMD, CMD, CMS, ataxia, HSP, neurogenetic disorders) and has resulted in new diagnoses and gene discovery. It is free and open for contributions from any rare disease clinician or researcher (info@rd-connect.eu).

**LAMBERT-EATON MYESTHENIC SYNDROME (LEMS) ASSOCIATED WITH SJÖGREN’S SYNDROME**

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Objectives/Background: The Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular disorder characterized by defective neurotransmitter release at presynaptic terminals of the neuromuscular junction. It is reported that up to 67% of the cases of LEMS are secondary to a neoplasm, especially small cell carcinoma of the lung. The remaining 33% have autoimmune LEMS or in conjunction with a rheumatologic disease. To our knowledge, LEMS associated with Sjögren’s syndrome is such a rare presentation.

Materials and Methods: A 54-year-old woman visited our clinic with complaints of dry mouth, muscle weakness of limbs and dizziness for 1 year. She had been treated as Sjögren’s syndrome about 1 month ago.

Results: The limb weakness was aggravated by activity. The neurologic examination revealed decreased deep tendon reflexes in all sites. In electrophysiologic studies, the amplitude of compound muscle action potential (CMAP) from the abductor digiti minimi (ADM) muscle is 2.6 mV (normal >5 mV) at resting state and 9.4 mV after 10-second exercise. In Jolly test, the amplitude of CMAP recorded on the ADM muscle increased (276%) during 50-Hz stimulation. Based on these findings, we made a diagnosis of LEMS. Chest CT showed no evidence of malignancy. She has been treated with 3,4-diaminopyridine for 6 months and showed some improvement of muscle weakness.

Conclusion: Sjögren’s syndrome should be considered as the cause of LEMS, especially in case with younger age of onset and with no underlying malignancy. We report a case of LEMS associated with Sjögren’s syndrome.
AP11

EPISODIC WEAKNESS: A FIVE-YEAR COMBINED ELECTRODIAGNOSTIC REVIEW FROM TWO CENTERS

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Objectives/Background: Episodic weakness is one of the major neurologic problems encountered in neurophysiology laboratories. Diagnostic tests such as nerve conduction studies - electromyography (EMG-NCV), single-fiber electromyography (SFEMG), repetitive nerve stimulation studies (RNSS), prolonged exercise test and short exercise test (PET-SET) for episodic weakness are the main diagnostic tests done to assist physicians in confirming their clinical diagnosis.

The aim of this study is to present electrodiagnostic profile of patients who underwent electrodagnostic procedures of the neurophysiology units of the University of Santo Tomas Hospital and Metropolitan Medical Center in the year 2012-2016 for episodic weakness.

Methodology: The investigators presented a descriptive study of the patients with episodic weakness who underwent electrodeagnostic procedures such as nerve conduction studies - electromyography (EMG-NCV), single-fiber electromyography (SFEMG), repetitive nerve stimulation studies (RNSS), prolonged exercise test and short exercise test (PET-SET) for episodic weakness. Electronic patient data were subjected to analysis to obtain patient demographics and electrodiagnosis.

Materials/Results: The number of patients who underwent EMG-NCV in our institutions was 3,899 combined. Most patients underwent RNSS (f =303), one-third of patients had post-synaptic myoneural junction disorder. For those who needed single-fiber EMG, results were positive and one patient had Lambert-Eaton Myasthenic Syndrome. Out of the 3,899 EMG-NCV done in both laboratories, fifty-four patients showed evidence of a myopathic disorder, while five patients had myotonia. Four out of the 25 patients who underwent PET-SET showed familial hypokalemic periodic paralysis and thyrotoxic paralysis. A significant number of patients who underwent PET-SET were normal studies.

Conclusion: Most patients referred to our laboratories utilised repetitive nerve stimulation studies for the evaluation of episodic weakness. For those with normal RNSS who needed single-fiber EMG, results turned out positive. The use of PET-SET in periodic paralysis is seldomly used despite its availability, given the prevalence of the disorder.

AP12

GUILLAIN-BARRÉ SYNDROME PRESENTING WITH ACUTE URINARY RETENTION AND T6 SENSORY LEVEL: A CASE REPORT

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Objectives/Background: Guillain-Barré syndrome (GBS) is an acute immune-mediated demyelinating disease. Early recognition of this disease is crucial as it can progress to life-threatening conditions such as respiratory failure or autonomic dysfunction. Typical clinical manifestations of GBS include progressive weakness of the limbs, bulbar, facial muscles and ophthalmoplegia. Sensory level and bladder dysfunction are more suggestive of myelopathy.

Materials and Methods: We report a case presenting with acute urinary retention and T6 sensory level. A diagnosis of GBS was established with the help of positive eletrophysiological study and negative spine magnetic resonance imaging (MRI).

Results: A 41-year-old gentleman with no past medical illnesses presented with a 3 day history of acute urinary retention and progressive lower limb weakness. His blood pressure and pulse rate were stable. Upon review, he had power 0/5 and areflexia in both lower limbs. He had a sensory level at T6. His cranial nerves were intact with negative cerebellar signs. Initial nerve conduction study (NCS) revealed absent F wave latencies in bilateral tibial and common peroneal nerves; and absent H-reflex. Spine MRI was normal. He was intubated for respiratory distress 2 days after admission and subsequently treated with plasmapheresis. We managed to discharge him with nasogastric tube and bladder catheter after 2 weeks of hospitalization. Upon clinic visit at 6 weeks, he completely recovered with no neurological sequelae. Repeated NCS was normal.

Conclusion: Sensory level and bladder dysfunction, though unusual, may present as the initial manifestations in GBS. NCS is useful in doubtful cases to add value to spine MRI to avoid diagnostic delay.
CEREBROTENDINOUS XANTHOMATOSIS: A CASE REPORT

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Background: Cerebrotendinous xanthomatosis (CTX) is a very rare autosomal recessive lipid storage disorder affecting bile acid biosynthesis. Pathogenic variants in CYP27A1 cause elevated cholestenol level in the body, which leads to a variable clinical manifestation, tendon xanthoma, cataracts, diarrhea, and neurological features.

Case: Herein, we describe the case of a 27 year-old Korean male who presented with gait difficulty, and intellectual disability. He was diagnosed with lumbar radiculopathy and medically treated for years, but gait difficulty had not been better. After several visits, we found his fusiform swellings of bilateral tendino-Achilles tendons. With a suspect of CTX, serum cholestenol level was checked and the level was increased. Genetic analysis resulted that the patient was heterozygous for the c.1214G>A (p.R405Q) and c.1420C>T (p.R474W) pathogenic variant, respectively in the CYP27A1 gene. Finally, we diagnosed him as CTX and replacement therapy has been done for 2 years. The CDCA treatment lead to a reduction of cholestenol and cholesterol biosynthetic precursors levels in plasma but his neurological disability was not recovered.

Conclusion: To the best of our knowledge, it is a first case of CTX in Korea.

A MYOPATHY WITH ANTI-SIGNAL RECOGNITION PARTICLE: FIRST RECORDED CASE IN THE PHILIPPINES

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Objectives/Background: Necrotizing autoimmune myopathy (NAM) is a fairly new disease entity that presents with subacute proximal weakness with a distinct histologic profile and auto-antibody. We report the first-well documented case of anti-SRP in the Philippines.

Materials and Methods: This is a case report.

Results: Patient is a 65 year-old female, no known co-morbidities and no family history of muscle disease, who initially complained of proximal body weakness, legs more than the arms in early 2014. She was initially diagnosed with an “early stage neuropathy” and underwent rehabilitation for two (2) months, with no improvement in symptoms. She then consulted our institution and was worked up for myopathy. Patient was given rosuvastatin in the latter part of 2015, but with no worsening of symptoms. Patient was given oral steroids, with stable degree of weakness. No immunotherapy given to the patient.

Her initial CPK-Total was very elevated, EMG-NCV showed a myopathic process. Rheumatologic work-up is negative. A paraneoplastic work-up was negative as well. Myositis panel was noted to be positive for anti-SRP. Muscle biopsy done and the final result was reflective of active necrotic and regenerating process, being compatible with the diagnosis of immune-mediated necrotizing myopathy associated with anti-SRP autoantibody. Patient was given oral steroids, with stable degree of weakness. No immunotherapy given to the patient.

Conclusion: We reported the first case of anti-SRP necrotizing myopathy in the Philippines. Immune-mediated necrotizing myopathy associated with anti-SRP autoantibody is a new and rare subset of inflammatory myopathy that should be considered in patients with a suspected inflammatory myopathy but with negative serologic work-ups. The diagnosis of anti-SRP myopathy is based on two parameters: 1) detection of anti-SRP antibodies in patient’s serum and, 2) histological diagnosis of inflammatory myopathy, usually of necrotizing myopathy.
FAMILIAL AMYLOID POLYNEUROPATHY IN MALAYSIANS

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Objectives/Background: Familial amyloid polyneuropathy (FAP) is a rare autosomal dominant peripheral neuropathy. We report a case series of Malaysian FAP patients.

Materials and Methods: This is a case series of patients with probable (positive sural nerve biopsy with family history) or definite (genetically confirmed) FAP seen at the University of Malaya Medical Centre between 2008 till 2017. The patients’ demographic and clinical features and investigations including nerve conduction studies and electromyography, echocardiography, sural nerve biopsy and hATTR mutation are reported.

Results: A total 10 index cases were seen. Of these, nine were ethnic Chinese and one ethnic Indian. There were 7 males (70%). Median age of onset of symptoms is 57.5 years (range: 41-66). Nine patients presented with numbness and weakness of the limbs while the other presented with postural hypotension. NCS/EMG showed sensorimotor polyneuropathy in all patients (four with associated carpal tunnel syndrome) and amyloid deposits were seen in the nerve biopsy in eight patients and endomyocardial biopsy in one and was diagnosed as familial amyloid cardiomyopathy (FAC). Six patients (60%) had abnormal cardiac echocardiogram. Five Chinese patients (83%) carried the Ala97Ser hATTR mutation while the FAC patient has Asp39Val mutation. The Indian patient had Gly67Val mutation. Another 3 patients have not had genetic testing yet.

Conclusion: FAP in Malaysians is seen mainly among ethnic Chinese and Ala97Ser may be a common mutation. Their age of onset is later, in middle age and the majority present with neuropathy symptoms although cardiac involvement is common.

VALOSIN CONTAINING PROTEIN (VCP)-RELATED MULTI-SYSTEM PROTEINOPATHY: AN UNDER-RECOGNIZED CAUSE OF DISTAL MYOPATHY WITH CLINICAL OVERLAP WITH HEREDITARY INCLUSION BODY MYOSITIS AND FRONTO-TEMPORAL DEMENTIA

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Objectives/Background: We present a patient with familial valosin containing protein (VCP) myopathy who later developed fronto-temporal dementia. Mutations in the VCP gene cause an autosomal dominant multisystem disease characterized by inclusion body myopathy (IBM)-like pathology associated with Paget’s disease of the bone (PDB) and fronto-temporal dementia (IBMPFD).

Materials and Methods: Case report.

Results: A 50 year old Caucasian man presented with progressive asymmetric distal > proximal muscle weakness since age 40. On examination there was winging of scapulae and bilateral foot drop (facioscapulohumeral muscular dystrophy-like phenotype). He had no sensory or bulbar symptoms. His mother had advanced dementia and a maternal uncle had died of ALS. EMG revealed an irritable myopathy with rare myotonic discharges. CK was normal. Muscle biopsy showed nonspecific changes with no evidence of inflammation or rimmed vacuoles. Work up for autoimmune myopathy, limb girdle muscular dystrophy panel (including hereditary IBM- GNE, Anoctamin 5 mutation), fascioscapular humeral muscular dystrophy and myotonic dystrophy was unremarkable. 8 years later he developed cognitive and behavioural impairments. In the setting of asymmetric distal muscle weakness, cognitive impairment, and a positive family history of dementia, valosin containing proteinopathy (VCP) causing myopathy was considered. Whole exom sequencing

**Conclusion:** VCP proteinopathy can be challenging to diagnose. VCPopathy should be considered in a patient with an asymmetrical distal weakness especially in the presence of personal or family history of dementia, motor neuron disease, or Paget’s disease of bone.

*Conclusion:* Laminopathies should be considered in patients presenting with marfanoid connective tissue disorder and congenital muscle disease.

**A NEW LMNA GENE MUTATION CAUSES LAMINOPATHY PRESENTING WITH A CONGENITAL MUSCLE DISEASE, COGNITIVE DYSFUNCTION AND MARFANOID CONNECTIVE TISSUE DISEASE**

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**Objectives/Background:** Lamin A/C is a major protein of the nuclear envelope. Mutations in the lamin A/C gene (LMNA) have been associated with a wide spectrum of phenotypes including congenital muscular dystrophy/ Emery Dreifus muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth neuropathy and Hutchinson - Gilford Progeria syndrome. We present a case of congenital muscle disease associated with marfanoid features and autism spectrum disorder with a novel LMNA gene mutation.

**Materials and Methods:** Case report.

**Results:** A 20 year male of Western European ancestry presented for evaluation of muscle weakness. He was hypotonic at birth. He was diagnosed with autism spectrum disorder and had mildly delayed motor milestones. He exhibited marfanoid features with a tall stature, long fingers, strabismus, high arched palate, kyphoscoliosis and osteopenia with a history of early fractures. Neurological examination revealed axial and generalized muscle weakness. Cardiac MRI showed dilated descending thoracic aorta at the sinobulbar junction with borderline aneurysmal dilation and mild aortic valve regurgitation. Creatine kinase, EMG was normal. MRI brain showed no white matter disease. Whole exom sequencing and genetic panel for connective tissue disorder was negative. Genetic panel for congenital muscular dystrophy revealed a novel heterozygous mutation in the LMNA gene (c.1634 G>A; p.Arg545His). In the literature, there is a report of a German patient with laminopathy due to a mutation in the cDNA location 1633 with amino acid change from arginine to cysteine.

**THE NEW ZEALAND NEUROMUSCULAR DISEASE REGISTRY; FIVE YEARS AND A THOUSAND PATIENTS**

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Objectives/Background: The New Zealand Neuromuscular Disease Registry has been recruiting for five years with a view to improved treatments for patients with neuromuscular disorders. Its primary aim is to enable participation in research including clinical trials and natural history studies. A developing aim of the Registry is to obtain molecular confirmation of diagnoses.

Materials and Methods: To achieve these aims the Registry operates as a longitudinal opt-in registry for both children and adults living with neuromuscular disease in NZ. Demographic, pre-specified, disease-specific clinical and genetic information is collected, curated and regularly updated. Data are stored securely with some data for specific disorders being housed offshore on secure platforms provided by collaborators.

Results: 1019 people have enrolled since the registry’s launch in August 2011 and, of these, eight have been involved in clinical trials, 134 in other disease-specific research and over 750 have contributed anonymised data to natural history studies. Sources of referral to the Registry include patient support organisations, with 181 self-referrals and 453 consented through fieldworkers; the Principal Investigator’s neurogenetic clinics (207); other neurologists (107); genetic services (47); and others (24).

Conclusion: The Registry has changed the face of neuromuscular research in NZ. Important factors in achieving this are the integral involvement of the patient support organisation and the minimal dependence upon clinicians, which can only occur with dedicated registry staff. By contributing data to natural history and feasibility studies, assisting in recruitment and advising researchers the Registry is now facilitating almost all neuromuscular research currently taking place in NZ.

DYSFERLINOPATHIES – A CLINICAL AND HISTOPATHOLOGICAL CORRELATION

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BACKGROUND: Miyoshi myopathy (MM) and limb girdle muscular dystrophy (LGMD2B) are distinct clinical entities and the risk of misdiagnosis and wrong treatment could be prevented by improving case definition. We describe the clinical features in 8 patients with dysferlin deficiency confirmed by muscle immunohistochemistry (IHC).

MATERIALS AND METHODS: Detailed clinical, biochemical and immunohistochemical analysis using antibodies against dystrophins, sarcoglycans, dysferlin B and Caveolin on muscle biopsies was carried out.

RESULTS: Of 8 patients (6 F, 2 M) presenting with manifestations of MM and LGMD2B, mean age of onset was 21 +/- 6.7 years and 19 +/- 4.5 respectively. Consanguinity was reported in 3 patients. Early and predominant involvement of calf muscles was reported in MM while weakness and atrophy of muscles of shoulder girdle and proximal lower-limb was noted in LGMD2B patients. Mean CK for both groups was 8,722 +/- 6483 IU/L. Muscle biopsy showed type 1 fiber predominance and dystrophic features with necrotic regeneration, variation in fiber size and evidence of inflammation. Negative dysferlin staining in all and secondary reduction of Caveolin-3 in 2 patients strongly suggested dysferlinopathy.

CONCLUSION: In our experience, dysferlinopathies formed nearly one third of patients with LGMD. Case definition is crucial for management in these cases. In resource constrained countries like Pakistan, careful clinical observations and muscle biopsy can be employed as primary tools for initial diagnosis and classification of such patients.

IMMUNOHISTOCHEMICAL AND GENETIC CHARACTERIZATION OF FEMALE DYSTROPHINOPATHY CARRIERS IN PAKISTAN

AP19

AP20
**Background:** Duchenne (DMD) and Becker (BMD) muscular dystrophies are the most common X-linked recessive muscular dystrophies. Dystrophin gene mutations usually affect men, but reportedly 6-8% of women are affected and are classified as symptomatic carriers. This study reports detailed clinical, histopathological and genetic characterization of 14 symptomatic female dystrophinopathy carriers.

**Methods:** Clinically, women with muscle weakness and/or dilated cardiomyopathy were classified as symptomatic carriers, while subjects with high serum creatine kinase (CK) levels and/or mild muscle cramps and myalgia were classified as asymptomatic. Muscle biopsy followed by immunohistochemistry with antibodies to dystrophins and sarcoglycans was carried out with beta spectrin control. Dystrophin gene analysis was carried out by multiplex ligation-dependent probe amplification (MLPA).

**Results:** Of the 14 included female carriers, 5 were symptomatic while 9 were asymptomatic. The mean age of symptom onset in the symptomatic and asymptomatic female carriers was 29.4 +/- 4.6 years and 22.3 +/- 6.8 years respectively. Serum CK levels were markedly elevated (mean: 1240 +/- 912 IU/mL) in symptomatic female carriers. Three of the symptomatic women had out-of-frame deletions (hotspots exons 2–20 and 44–53) while two had duplications. Of the nine asymptomatic female carriers, 7 had out-of-frame deletions while 2 had duplications.

**Conclusions:** Female dystrophinopathy affects the prevalence of DMD/BMD in males; hence early diagnosis and appropriate genetic counselling are needed especially in patients with a negative family history. Screening with MLPA is useful because it helps in accurate diagnosis in female patients previously wrongly diagnosed as limb-girdle muscular dystrophy, inflammatory myositis, or an unknown myopathy.
Results: 22 patients (male-19; Female-3) were included. 4 were familial and 18 were sporadic. All had motor > sensory, distal > proximal weakness affecting LL > UL. Pes cavus in 19 and Scoliosis was evident in 1 patient each. Electrophysiology showed 15 demyelinating and 7 axonal patterns. Multifocality was seen in 5 patients. MRI of 6 out of 10 patients showed thickened plexuses and roots. Molecular diagnosis was achieved in 13 patients (63.07%) out of which 3 PMP22, 2 GJB1, 2 SH3TC2, 2 HSPB1 and 1 mutation in each SPTLC2, MPZ, AARS and NEFH genes was observed.

Conclusion: Our results describe different mutational patterns in CMT cohort with phenotype and electrophysiological correlation. Radiological evaluation has a potential of complementary or alternative strategy to neurophysiology. Targeted multigene panel testing reveals high heterogeneity with significant overlap of genotype-phenotype patterns. It is well recommended over sequential genetic testing as comprehensive and cost effective tool in genetically heterogeneous population like India.

ADULT INHERITED MYOPATHIES IN A TERTIARY GENERAL HOSPITAL, MYANMAR

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Objectives/Background: In addition to history, examination, creatinine kinase and electromyography, diagnosis of specific inherited myopathies requires muscle histology and genetic analysis, both of which require advanced pathology and genetic laboratory facilities. Yangon General Hospital (YGH) is one of the biggest tertiary center in Myanmar, yet our neuromuscular service is quite infantile. Electromyography service was started in October 2014. Previously, only paraffin H and E stain was used. Starting from December 2015, when Dr Nishino from Japan gave hands on training on taking muscle biopsy and freezing specimens, onwards, we could have started frozen sections. Here, we describe the adult inherited myopathy cases presented to department of neurology, YGH, from November 2014 to April 2016. Our aim is to get a rough idea of the distribution of various types of inherited myopathy cases in Myanmar by looking into cases presented at the main referral center.

Materials and Methods: All inherited myopathy cases presented to department of neurology, YGH, over one and a half year period from November 2014 to April 2016 were studied.

Results: Total 18 patients were collected over the study period. These include 3 myotonic dystrophies (type 1), 3 facioscapulohumeral muscular dystrophies (FSHD), 3 Duchenne muscular dystrophies (DMD), 1 Miyoshi distal myopathy, 1 GNE myopathy, 1 laminopathy, 1 calpainopathy, 1 Ullrich congenital muscular dystrophy and 2 unclassified LGMD.

Conclusion: In accordance with other countries’ data, myotonic dystrophy, FSHD and dystrophinopathies were found to be the most common types of inherited myopathies in Myanmar.

A REPORT ON TWO CASES OF CENTRONUCLEAR MYOPATHY

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Objectives/Background: Centronuclear myopathy (CNM) is a rare inherited neuromuscular disorder characterized by clinical features of a congenital myopathy and centrally placed nuclei on muscle biopsy. Although the pathological findings are uniform, the clinical features and genetic background are heterogeneous.

Materials and Methods: We reviewed a retrospective data of two patients. First case was an eighteen year old man whom presented with proximal muscle weakness since age 7 years old. There was no family history or consangunuity. Clinically he had bilateral partial ptosis, ophthalmoparesis with mild proximal muscle weaknesses with muscle power grade 4/5 over the both shoulders and thighs. His creatinine kinase was raised at 472U/L. Muscle biopsy showed marked variability in fiber size, numerous central nuclei with...
echocardiogram and lung function test were normal. Our second case was a 36-year-old lady whom presented with gait disturbance since age 9 years. She became wheelchair bound at the age 16. No history of consanguinity. She had normal cognition. Examination revealed myopathic facies with bilateral partial ptosis. No ophthalmoparesis. Muscle power over both shoulders grade 3/5 and 2/5 over both thighs with presence of contractures. The electromyography showed myopathic changes and muscle biopsy showed similar findings as our first case with presence of necklace fibers. Her lung function test showed restrictive patterns.

Results: Not available

Conclusion: Clinical picture of CNM is highly variable. Genetic testing is recommended however it is not widely available. Management is mainly supportive, hence genetic counselling should be offered to all patients and families in whom a diagnosis of CNM has been made.

BILATERAL POLYRADICULITIS FOLLOWING EPIDURAL ANALGESIA WITH BUPIVACAINE

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Objectives/Background: Neurological injuries (traumatic or non-traumatic) secondary to central neuraxial block are extremely rare. The anatomical site of damage could be the spinal cord, nerve roots or spinal vasculature. The occurrence of neurological symptoms after spinal anaesthesia has been reported with several local anaesthetics including lidocaine, prilocaine, mepivacaine, tetracaine and rarely with Bupivacaine.

Case: A 42 year old male developed rapid onset bilateral leg weakness following epidural analgesia which he was receiving for post-operative pain control. He had undergone partial Gastrectomy for locally advanced gastric carcinoma. On examination he had bilateral flaccid paralysis of legs, areflexia in lower limbs and variable sensory impairment up to T 9 dermatome. MRI spine did not reveal any compression initially. Nerve conduction study demonstrated abnormal motor NCS with either no response or very low amplitudes in lower limbs. Repeat MRI spine after 4 weeks demonstrated thickening and radiation of intermyofibillary network from the centre fibers. His enhancement of cauda equina nerve roots representing radiculitis. Patient is currently bedbound with no significant improvement in his neurological status.

Conclusion: Although generally a safe procedure with low frequency of complications, lumbar epidural anaesthesia or analgesia occasionally causes neurologic sequelae such as radiculopathy. Patients should be made aware of this rare but seriously debilitating complication before administration of epidural anaesthesia.

OBJECTIVES/BACKGROUND: Spinobulbar muscular atrophy (SBMA), also known as Kennedy disease, manifest as motor weakness and wasting of facial, bulbar and limb muscles. Hereditary neuropathy with liability to pressure palsy (HNPP) is characterized by recurrent sensory or motor dysfunctions that are typically precipitated by minor trauma or compression. The combination of these two diseases in a same patient is extremely rare. We report a case of simultaneous clinical features of SBMA and atypical HNPP, with genetic confirmation of CAG expansion in the androgen receptor (AR) gene and deletion of the peripheral myelin protein 22 (PMP22) gene.

Materials and Methods: A 62-year-old man presented with a 23-year-history of intermittent fasciculation in the bilateral upper limbs and trunk. He reported progressive muscle weakness in all limbs with dysesthesia predominantly in the distal regions. On neurological examination, SBMA was suspected due to postural upper limb tremor, weakness, perioral fasciculation and atrophy with weakness in the upper and lower limbs. However, some findings were not consistent with SBMA, such as distal dominant weakness and prominent atrophy of intrinsic foot muscles with hammer toes. The patient’s deep tendon reflexes were absent in all limbs.
**Results:** The electrodiagnostic examination showed demyelinating sensorimotor polyneuropathy. Simultaneous HNPP and SBMA were suspected and relevant genetic testing revealed deletion of the PMP22 gene and CAG repeats in the AR gene.

**Conclusion:** Detailed patient histories, as well as neurological and electrophysiological examinations will help to diagnose a patient with two rare genetic diseases at the same time.

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**A DYSFERLINOPATHY MOUSE MODEL WITH NONSENSE MUTATION TREATED WITH READTHROUGH THERAPY**

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**Objectives/Background:** Mutations in the dysferlin gene cause limb-girdle muscular dystrophy 2B or Miyoshi distal myopathy with autosomal recessive inheritance pattern. A few mouse models harboring truncating mutations have been in use for the research of the dysferlinopathy. We found nonsense mutations are most common among Korean patients with dysferlinopathy; more than half of the patients have at least one nonsense allele, which could be mitigated by readthrough strategy.

**Materials and Methods:** We generated a knock-in mouse with p.Q832* mutation, most frequently found among our dysferlinopathy cases. The mice were back-crossed to C57/BL6 over 5 generations.

**Results:** Mice with homozygous p.Q832* mutation, named dqx, performed poorer on Rotarod and treadmill test than wild type C57BL6 mice and moved less on activity monitoring. On eccentric contraction ex vivo, extensor digitorum longus muscle from dqx tended to break easily on the first few contractions. All these abnormality could successfully be alleviated when the mice were administered with gentamicin for 3 weeks.

**Conclusion:** These results support that readthrough strategy may also be applicable to nonsense dysferlinopathy patients.

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**GENETIC SPECTRUM AND NATURAL HISTORY OF GNE MYOPATHY IN 29 KOREAN PATIENTS**

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**Objectives/Background:** GNE myopathy is recently considered as a treatable disease since sialic acid supplementation is available and effective. Thus, now we need to investigate genetic and clinical spectrum and disease progression of the disease.

**Materials and Methods:** We recruited 29 patients with recessive GNE mutations. Clinical information was collected on direct visit or phone calls. Genetic spectrum and clinical data were analyzed to get a relationship between clinical and genetic features and disease progression.

**Results:** Eleven mutations were detected from 58 alleles. The most common mutation was c.1807G>C (p.V603L in 29 alleles) and c.131G>C (p.C44S in 16 alleles). Two of novel mutations were found. Onset ages were 26±9 years old (14–51 years). As an initial symptom, climbing difficulty/waddling gait suggestive of proximal leg weakness was the most common (12/29, limb-girdle phenotype) and foot drop was the next (8/29, distal phenotype). The number of joints that can move against gravity was decreased in proportion to disease duration (r²=0.6747). Loss of ambulation occurred 10 years later from the onset. Specifically, among wheelchair-bound patients disease duration was longer in patients with limb-girdle phenotype than in patients with initial foot drop. However, the difference depending on the location of mutations (epimerase + kinase vs. kinase domain) was not shown.

**Conclusion:** Our patients with GNE myopathy appeared to be somehow homogeneous in genetic spectrum of GNE mutations. It is notable that limb-girdle phenotype is more common as described earlier, and the disease progression seemed to be relatively consistent among our patients. This study provides the information about natural courses of Korean patients with GNE myopathy.
A FAMILIAL CASE OF VCP-RELATED MOTOR NEURON DISEASE

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Objectives/Background: The VCP gene encodes valosin-containing protein, a ubiquitously expressed multifunctional protein. It involves in multiple cellular functions ranging from organelle biogenesis to ubiquitin-dependent protein degradation. Its dysfunction causes several phenotypes encompassing inclusion body myopathy with Paget disease of bone and frontotemporal dementia (IBMPFD), amyotrophic lateral sclerosis with or without frontotemporal dementia, and Charcot-Marie-Tooth disease.

Materials and Methods: A 49-year-old man presented with 6 months of progressive limbs weakness. He felt difficulty in going up the stairs and walking a distance as before. He could still manage his daily activities. Physical examination revealed proximal dominant leg weakness without sensory deficit, yet normoactive deep tendon reflex without pathologic reflex. Mild non-progressive dysarthria was also accompanied. Blood laboratory findings were all within normal limits. Needle EMG confirmed a widespread denervation and reinnervation process. One out of his 3 brothers also had progressive leg weakness.

Results: Familial motor neuron disease was suspected and gene sequence analysis revealed a variant c.463C>T (p.R155C) in VCP gene, previously reported in a Korean family with IBMPFD.

Conclusion: We report a case of VCP-related motor neuron disease with VCP p.R155C mutation, known to cause IBMPFD. However, a phenotype of pure motor neuron disease expands the spectrum of the same mutation. Search for the genetic variant is suggested on evaluation of slowly progressing generalized motor neuron disease.

A FAMILY OF MOUNDING MUSCLE DISEASE WITH A CAV3 MUTATION

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Objectives/Background: Caveolin-3 is a membrane protein in sarcolemma which has been identified to stabilize sarcolemma and modulate signal pathways. Five clinical features of caveolinopathy have been described. Here we report a genetically confirmed family with caveolinopathy presenting as exercise induced stiffness and transient focal muscle mounding.

Materials and Methods: A 20-year old man complained transient stiffness in his extremities for 10 years. While he exercises, power loaded muscles became stiff with focal muscle mounding. Wakeup stiffness, hit-induced myoedema was infrequently accompanied by rippling. His maternal grandmother, mother, uncle and elder brother had these symptoms in common. Tap-induced muscle mounding can be elicited on examination and calf hypertrophy was bilateral without myopathic face, dystonia, or muscle weakness.

Results: Creatinine kinase was constantly high up to 5 times normal upper limit. Chronic myopathic pattern in needle electromyographic findings were present. Interestingly, tapping on the muscle with EMG needle inserted induced spontaneous activities. There were no myotonic discharges or decremental responses in short exercise test. Muscle biopsy revealed moderate fiber size variation, regenerating fibers and internal nuclei. Focused exome sequencing of CAV3 gene confirmed a known pathogenic mutation, c. 80G>A (p.R27Q), heterozygously from the symptomatic members of the family.

Conclusion: We report caveolinopathy presenting as exercise induced stiffness and muscle mounding without motor weakness which can be initially misunderstood myotonic disorders. Autosomal dominant inheritance was confirmed phenotypically and genetically through the family. This is a second report of genetically confirmed caveolinopathy patient in Korea.
### THE FAT1 ALTERATION IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY TYPE 1

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**Background:** Facioscapulohumeral muscular dystrophy type 1 (FSHD1) is caused by contraction of the D4Z4 repeat array on the chromosome 4q to size 1-10 units. The clinical severity of FSHD1 was inversely correlated with D4Z4 repeat units. However, most FSHD1 patients carry 1 to 6 D4Z4 repeat units and 1 - 3% of the healthy control populations also carry 8 to 10 repeat units. Previous studies revealed that the FAT1 expression is associated with disease activity of FSHD1 and the FAT1 alterations result in hereditary myopathy with a FSHD-like phenotype. Here, we present a Korean FSHD1 patient with eight D4Z4 repeat units and a FAT1 mutation.

**Case report:** A 59-year-old woman presented to our neurologic clinic with proximal muscle weakness. She did not have a family history of any neuromuscular disorders. Her serum creatine kinase level was 140 IU/l (reference value: <135 IU/L). Needle electromyography was compatible with generalized myopathy. We performed Southern blot analysis for determining D4Z4 contraction size. We identified the shortening of the D4Z4 allele, but eight repeat units were also found in healthy subjects. Therefore, we performed targeted sequencing of modifier genes (SMCHD1, DNMT3B and FAT1). We identified the c.10331 A>G (p.N3444S) variant in FAT1.

**Conclusion:** Our study is the first report of coexistence of the contracted D4Z4 repeats and FAT1 mutation in a FSHD1 patient. This finding suggests that the FAT1 alterations work as genetic modifiers of disease severity in FSHD.

### INFLAMMATORY MYOPATHY

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**Objectives/Background:** Acute muscle pain and walking difficulty are symptoms compatible with both benign and severe degenerative diseases. It is important to better define differential diagnoses in cases of muscle pain and walking difficulty in children. Benign acute childhood myositis (BACM) and Guillain–Barré syndrome (GBS) should be considered in the differential diagnoses in such situations. However, concurrence of BACM and GBS in children is uncommon in the literature.

**Materials and Methods:** We report a 3-year-old girl who developed BACM and GBS following parainfluenza virus type 1 infection.

**Results:** She was referred to our hospital for further evaluation of walking difficulty. A multiplex RT-PCR in nasal swab revealed parainfluenza virus type 1 infection. Elevated CPK, LDH and AST strongly suggested the presence of myositis. The high CK that was detected in the admission was suggestive of myositis. However, decreased DTR and muscle weakness were regarded as atypical features in myositis. After all, the EMG findings revealed the coexistence of acute inflammatory demyelinating polyneuropathy, and intravenous immunoglobulin was additionally described for the treatment of GBS. The symptoms were rapidly improved. One week later, the distal muscle weakness of the lower extremities disappeared, the patellar tendon reflexes were improved and the neurologic examinations revealed normal findings.

**Conclusion:** To our knowledge, this is the first case of simultaneous BACM and GBS caused by parainfluenza virus. This case demonstrates the need to consider concurrence of musculoskeletal and nervous system involvement in pediatric patients with walking difficulty.
THE USAGE OF DPP4 INHIBITORS IN DIABETIC PATIENTS WITH MYOTONIC DYSTROPHY: A QUESTIONNAIRE SURVEY UTILIZING THE PATIENT REGISTRY DATABASE

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Objectives/Background: Dipeptidyl peptidase 4 inhibitors (DPP4-I) are widely used for the treatment of type 2 diabetes mellitus. DPP4-I inhibit the degradation of the incretins, so has an advantage of the very low risk of hypoglycemia. However, the efficacy against diabetic patients with myotonic dystrophy (DM) has not been verified. The aim of the study was to investigate the usage of DPP4-I in patients with DM.

Materials and Methods: DM patients with diabetes mellitus registered to the Japanese national patient registry (Remudy) were extracted from the Remudy database. Questionnaires about therapeutic situation for glucose intolerance were sent by post to both of the patients and their attending doctors for diabetic tract medicine.

Results: Sixty patients were participated. The response rate was 48%. The mean age of patients was 50 +/- 12 years (+/- SD). Twenty of sixty patients were treated by DPP4-I. At 12 months after introducing DPP4-I in eighteen of twenty patients, the mean HbA1c was decreased from 8.5 +/- 1.8 to 7.5 +/- 1.2 (%), fasting blood sugar lowered from 145 +/- 37 to 140 +/- 51 (mg/dl), and weight reduced from 64.8 +/- 6.8 to 62.7 +/- 6.3 (kg). Two patients interrupted intake of DPP4-I because of prominent improvement of glycemic control or poor effectiveness. No serious adverse effects were reported.

Conclusion: DPP4-I have been efficaciously used in one-third DM patients complicated with diabetes mellitus without major adverse effects. DPP4-I could be a useful therapeutics against diabetic patients in DM.

CLINICAL FEATURES OF ANTI-SRP AND ANTI-HMGCR NECROTIZING MYOPATHY IN MALAYSIANS

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Objectives/Background: To describe the clinical features of immune-mediated necrotizing myopathy (IMNM) associated with anti-signal recognition particle (SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies in Malaysian patients.

Materials and Methods: We examined a cohort of 328 patients with idiopathic inflammatory myopathy (IIM) presented to University of Malaya Medical Centre from December 2012 to October 2016. Anti-SRP and anti-HMGCR antibodies were determined by RNA immunoprecipitation and ELISA respectively.

Results: Of 306 patients with IIM (after excluding 22 inclusion body myositis), 101 (33%) were having IMNM based on serology and muscle pathology. Of these 101 patients, 40 were tested for myositis specific autoantibodies. The frequency of anti-SRP and anti-HMGCR antibodies was 45% (18/40) and 22.5% (9/40) respectively. Two patients had dual positivity. Mean age of onset (40.3 ± 15.4 vs 32.6 ± 13.8) was not different between the 2 groups. Female (87.5%) was more common in the anti-SRP group.
whereas equal sex distribution in anti-HMGCR group. Malay (50%) and Chinese (43.8%) were found more frequently in the anti-SRP group whereas only Malay (57.1%) was more common in anti-HMGCR group. Skin rash (57.1% vs 12.5%; p=0.025) was more common and serum creatine kinase (CK) level (21543 ± 24525 vs 6708 ± 4848; p=0.027) was markedly higher in patients with anti-HMGCR antibodies than in those with anti-SRP antibodies. Statin exposure, severe muscle weakness, neck weakness, dysphagia, myalgia, joint pain and neurological outcome were not different in the 2 groups.

**Conclusion:** Anti-HMGCR antibodies were associated with skin rash and higher level of CK level. Majority of the patients shared the common features between the anti-SRP and anti-HMGCR.

**HISTOPATHOLOGICAL, SEROLOGICAL AND HLA ASSOCIATION PROFILE OF MYOPATHY AGAINST HMGCR ANTIBODIES IN MALAYSIAN PATIENTS**

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**Background:** Immune-mediated necrotising myopathy (IMNM) is characterised by proximal muscle weakness, elevated serum creatine kinase and prominent necrosis on muscle biopsy. IMNM in some patients is associated with the presence of antibodies against signal recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR).

**Objective:** To investigate the histopathological, serological and the HLA association profile of anti-HMGCR myopathy in Malaysian patients.

**Materials and Methods:** Twenty-four patients with biopsy-proven IMNM were tested for antibodies against HMGCR and SRP using ELISA and RNA Precipitation, respectively. Blood DNA from six patients with anti-HMGCR antibodies were HLA genotyped for class II alleles using the low-resolution single-specific primer-polymerase chain reaction (SSP-PCR). The odds ratios (OR), 95% confidence intervals (95% CI) and P-values to test for significance were computed using SPSS.

**Results:** Nine patients (37.5%) were positive for anti-HMGCR antibodies. The majority (55.6%) were female. They comprised of four (44.5%) ethnic Malay, three (33.3%) ethnic Indian and two (22.2%) ethnic Chinese. On muscle biopsy, all patients showed prominent necrosis. Seven (77.8%) patients showed minimal endomysial inflammation, while three had moderate inflammation. Interestingly, two patients were also positive for SRP antibodies, while one had RO-52 antibodies. The HLA genotyping showed an association with HLA-DQB1*02 allele (P = 0.0033, OR = 28.84, 95% CI = 3.0 – 280.0), HLA-DRB1*03 allele (P = 0.0482, OR = 27.38, 95% CI = 2.8 – 268.1) and HLA-DRB1*09 allele (P = 0.0086, OR = 25.0, 95% CI = 3.5 – 178.8) in Malay patients.

**Conclusion:** Our findings suggest that anti-HMGCR myopathy may be associated with DQ2, DR3 and DR9 in Malays.
QUANTIFYING THE DEGREE OF FATTY INFILTRATION OF MUSCLE WITH TEXRAD ANALYSIS OF MRI IMAGES

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Objectives/Background: Patients with muscle disease can have fatty infiltration of muscle and the degree of fatty infiltration is currently made by visual inspection. We aim to evaluate if TexRAD analysis is able to quantify the degree of diseased muscle by comparing the ratio of muscle to subcutaneous fat in diseased muscle and normal muscle, higher ratios indicating greater degree of fat infiltration.

Materials and Methods: In this IRB approved prospective study, patients with muscle disease referred by neurologists and subjects with no muscle disease were scanned on a 3T MRI scanner. All had T1 weighted coronal scans of the lower limbs which were reformatted into axial images for analysis.

Single operator manually outlined separately the muscle and subcutaneous fat of all patients and controls on cross sections of the mid thigh and mid calf using TexRAD software. Ratios of muscle to subcutaneous fat were generated and values between patients and controls were compared.

Results: There were 16 patients and 12 controls who underwent MRI. Ratios of muscle to subcutaneous fat signal in controls of 0.51+/-0.06 for right thigh, 0.55+/-0.06 for left thigh, 0.52+/-0.05 for right calf, 0.55+/-0.05 for left calf

The patients had higher ratios of 0.61+/-0.11 for right thigh, 0.64+/-0.12 for left thigh, 0.62+/-0.12 for right calf, 0.64+/-0.12 for left calf. The increased ratios exhibited by patients compared to controls are statistically significant (p<0.01).

Conclusion: Children with muscle disease show fatty infiltration of muscle on MRI and this can be quantified as increased muscle to subcutaneous fat signal.

ADSS1 MYOPATHY IN KOREAN PATIENTS

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Objectives/Background: Distal myopathy is a heterogeneous group of hereditary muscle disorders presented by progressive muscular weakness beginning in distal muscles. ADSS1 gene mutation, which was recently reported by our group firstly, is one of the causative genes responsible for distal myopathy. ADSS1 myopathy is characterized by autosomal recessive pattern. We aimed to investigate clinical manifestations of ADSS1 myopathy and elucidate mutation spectra.

Materials and Methods: Eleven patients from nine unrelated families were diagnosed with ADSS1 myopathy via direct or targeted sequencing of the ADSS1 gene. Clinical, mutational, radiological and pathological spectra were then analyzed.

Results: We identified three different mutation in ADSS1 gene (c.910G>A, c.1048delA and c.1220T>C). Ten patients had ADSS1 gene variants with c.910G>A and c.1048delA, which are most common variant of the ADSS1 gene.

Clinically, patients with ADSS1 mutations demonstrated distal muscle weakness in adolescence, followed by quadriceps muscle weakness in the early 30s. All patients had mild facial weakness and two patients complained of easy fatigue while eating and chewing.

Pathologically, vastus lateralis muscle biopsies revealed non-specific chronic myopathic features with a few nemaline rods.

Whole body muscle MR imaging showed more fatty replacement in the distal limb and tongue muscles than in the proximal limb and axial muscles.

Conclusion: We identified three different ADSS1 mutations in Korean patients and demonstrated clinical, pathological and radiological findings. ADSS1 myopathy was not rare among distal myopathy in patients of Korean origin, and expanded the clinical and genetic spectrum. Therefore, we suggest that the screening test of ADSS1 gene should be considered for the diagnosis of distal myopathy.
EVALUATION OF THE RELIABILITY OF PATHOLOGICAL CLASSIFICATION CRITERIA FOR ADULT IDIOPATHIC INFLAMMATORY MYOPATHIES WITH IN DEPTH ANALYSIS OF MUSCLE BIOPSIES

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Objective: To explore the reliability of the 2004 ENMC classification criteria for idiopathic inflammatory myopathies (IIMs) with in depth analysis of muscle biopsies, and subsequent comparison of the clinical characteristics among polymyositis (PM), non-specific myositis (NSM) and immune-mediated necrotizing myopathy (IMNM).

Materials and Methods: We conducted a retrospective analysis of 57 IIM cases with the exception of dermatomyositis (DM) and sporadic inclusion body myositis (sIBM). Subgroups of these non-DM/sIBM-IIM patients were classified after a comprehensive investigation of biopsy findings on three levels with 50-slide interval.

Results: In 57 non-DM/sIBM-IIM patients, 25 were classified as PM, 15 as NSM and 17 as IMNM. For the 51 patients that underwent multilevel sectioning, evaluation of the pathological changes on different levels led to rectification of subgroup diagnosis in 11 patients. Four PM were reclassified as NSM and 7 NSM as IMNM. Inclusion of atypical CD8+ T cell surrounding non-necrotic muscle fibers resulted in reclassification of 2 patients from NSM to PM. Employing 20 lymphocytes as the cut-offs of perivascular infiltration instead of 10 resulted in recategorization of 9 patients from NSM to IMNM. No differences in age of onset, sex, disease duration, distribution of muscle weakness or treatment outcomes were identified among the subgroups.

Conclusions: Pathological changes proposed by the 2004 ENMC criteria do not suffice to accurately distinguish the subgroups of non-DM/sIBM-IIM patients on single muscle sectioning. The similar clinical manifestation and treatment outcomes suggest the subclassification of non-DM/sIBM-IIM based on cellular infiltration pattern is of limited clinical significance.

THE CLINICAL FEATURES OF STATIN-NAÏVE ANTI-HMGCR ANTIBODY-ASSOCIATED NECROTIZING MYOPATHY IN CHINA

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Objective: Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have been associated with immune-mediated necrotizing myopathy (IMNM). Some studies have observed difference between statin-exposed and statin-naïve anti-HMGCR-antibody-associated IMNM patients. As the data concerning clinical features and treatment in statin-naïve patients are very limited, we aimed to clarify the phenotypes and therapeutic strategies of statin-naïve patients.

Methods: We detected anti-HMGCR antibodies for 98 patients who satisfied the ENMC criteria for idiopathic inflammatory myopathy and had negative anti-signal recognition particle protein (SRP). We subsequently re-assessed the clinical and pathology features of the patients with positive anti-HMGCR...
antibodies.

**Results:** We identified 21 statin-naive patients with anti-HMGCR antibodies (21.4%). The ratio was significantly higher than other studies. In our cohort, the mean onset age was 35.3 ± 20.1 years old. Proximal lower limbs and neck flexor muscle were most severely involved. As for muscle imaging, 81.3% (13/16) patients showed posterior thighs involvement, within whom three patients also had anterior thighs involvement and limb-girdle muscular dystrophy-like clinical features. The recurrence rate of our cohort was 38.1%. Meanwhile 61.9% patients needed combined immunosuppressive therapies. We also found that the early-onset patients (<50 years old) had higher CK levels, recurrence rate and combined immunosuppressive therapy rate than late-onset patients (>50 years old).

**Conclusion:** Statin-naive anti-HMGCR antibody-associated IMNM may not be rare. For these patients, the onset age may be younger than statin-exposed patients. With respect to statin-naive patients, early-onset patients had different clinical features and therapeutic response from late-onset patients. For early-onset patients, we should take it seriously because limb-girdle muscular dystrophy-like features may interfere with the diagnosis and treatment, and the detection of anti-HMGCR antibody was important.

**A CASE OF RECURRENT SEIZURE AND EXERCISE INTOLERANCE**

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The patient is an 18-year-old female presenting with recurrent seizure and exercise intolerance for 18 years.

She was hospitalized for recurrent seizure and unconsciousness twice at the age of 12 and 13, and showed little response to antiepileptic drugs. Besides, she was found hypocalcemic. Seizures relieved after given calcium supplements. At the age of 18, she felt difficult in long time walking and needed to take a rest every 5 minutes. Symptoms progressively worsened and reached the worst status 3 months later. At that time, it was hard for her to stand up, raise head, chew and swallow food and speak clearly.

This patient is a child of unconsanguineous parents with a negative family history. Though delivered normally without any history of ischemia and hypoxia, the patient presented with developmental delays and congenital cardiac malformation. She was unable to walk and speak till the age of 2. Meanwhile her parents noticed her abnormal walking posture which was more obvious at the left side. She also presented with learning difficulties, especially in mathematics, and thus didn’t finish her junior high school. She was diagnosed as tetralogy of Fallot at the age of 4 and underwent cardiac surgery two years later.

When she was first seen by us at the age of 18, she has a height of 155cm and a weight of 43kg weight. She had a deficient intelligence with a MMSE score of 20. Physical examination showed remarkable cognitive delay, slurred speech, high palate and paravertebral muscle atrophy. The left limbs were shorter than the right. She presented with joint contractures in elbows, wrists, ankles and knees and the left more severe than the right. Muscle mass was abnormal with mildly elevated muscular tone in the left side and decreased muscle strength especially in neck and proximal limbs. Deep tendon reflexes were generally 1+. Pyramidal signs were negative. There was mild ataxia with a bad performance in finger-nose test and heel-knee-tibia test.

Blood electrolytes were normal except that the level of serum calcium was decreased to 1.52mmol/L (2.10-2.60mmol/L) and the serum phosphorus was elevated to 2.6mmol/L (0.80-1.60mmol/L). Parathyroid hormone was slightly decreased to 10.6ng/L (11.0-67.0ng/L). Serum creatine kinase was slightly elevated to 308U/L (38-174U/L) and the level of LDH was elevated to 932U/L (125-225U/L). Brain MRI revealed cortex malformation, cerebellar atrophy and lesions in the basal ganglia. EMG detected myogenic changes with normal NCS. Muscle MRI showed remarkable edema in bilateral lower limbs. Muscle biopsy was normal.
LONG-TERM FOLLOW-UP OF THREE CHILDREN WITH COLQ RELATED CONGENITAL MYASTHENIC SYNDROME OF DIFFERENT MUTATIONS RESPONSIVE TO SALBUTAMOL

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Objectives/Background: Congenital myasthenic syndromes (CMS) are a group of rare inherited disorders characterized by impaired neuromuscular transmission. Mutations in the acetylcholinesterase (AChE) collagen-like tail subunit gene (COLQ) cause recessive forms of CMS causing end-plate AChE deficiency.

Materials and Methods: We present 3 children with different COLQ -mutations treated with salbutamol and followed up for 2 - 10 years. All three children have ptosis, muscle weakness, easy fatigability, and diagnostic electrophysiological findings with decremental response at low-frequency motor nerve stimulation and positive repetitive compound muscle action potentials.

Results: All the 3 children showed significant improvement in motor performance and extra-ocular movements after salbutamol but minimal change in bilateral eyelid ptosis. There was no observed side effect. The most severely affected child with a homozygous exon 14 and partial exon 15 deletion in COLQ gene has early infantile onset of significant generalized weakness required ventilator support and gastrostomy feeding before salbutamol therapy. Exon 14 and part of exon 15 are translated into the C-terminal domain of the COLQ in a region that interacts with the muscle-specific kinase (MUSK) and helps anchoring the endplate AChE to the basal lamina. Deletion in this region hence is expected to cause pathogenic AChE deficiency. On the other hand, the child with the mildest presentation of mainly predominant limb girdle weakness and no respiratory involvement had two splice site mutations.

Conclusion: Long term oral salbutamol therapy can significantly improve and maintain the motor performance of the three affected children with different type of COLQ mutation. The clinical severity of the COLQ-related CMS could be related to the type and site of mutations.

A COMPARATIVE ANALYSIS OF EARLY ELECTROPHYSIOLOGICAL FINDINGS OF ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (AIDP) VARIANT OF GBS WITH THE GLOBAL DATA

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Objectives/Background: Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common subtype of Guillain Barre Syndrome (GBS) in Pakistan. The early electrophysiological findings in first 2 weeks and their comparison to the global data has not been studied.

Materials and Methods: The charts of 87 patients, diagnosed as AIDP on clinical grounds and nerve conduction studies during 5 years, were studied. Patients with concomitant diseases causing neuropathies like diabetes, hypothyroid, vitamin B12 deficiency,
exposure to chemotherapeutic drugs were excluded.

**Results:**
- Decreased Compound muscle action potentials CMAP’s 85%
- Slow conduction velocities 75% prolonged latency 71% of motor nerves.
- Absent H-Reflexes 65%
- Temporal dispersion 64% and conduction block 52%
- Absent 48%, and prolonged F-wave responses 39%
- Prolonged sensory latencies 48%.
- Sural sparing pattern 73%, with median sensory nerve the most.
- Abnormal Blink reflex in 37%.
- Fibrillation potentials and sharp waves 90% in EMG in cases with very low CMAPs.
- 9 patients with very low CMAPs at presentation needed intubation.

**Conclusion:**
- Increased frequency of very low CMAP’s/SNAP’s, prolonged distal latencies and temporal dispersion/conduction blocks.
- Higher number of Sural sparing pattern.
- No significant differences in Conduction velocities and H/F-responses
- Blink reflex can help in the diagnosis of AIDP.
- Needle EMG in early disease should be considered in those with very low CMAP’s.
- A follow up study is recommended for prognosis and rule out axonal variant of GBS.